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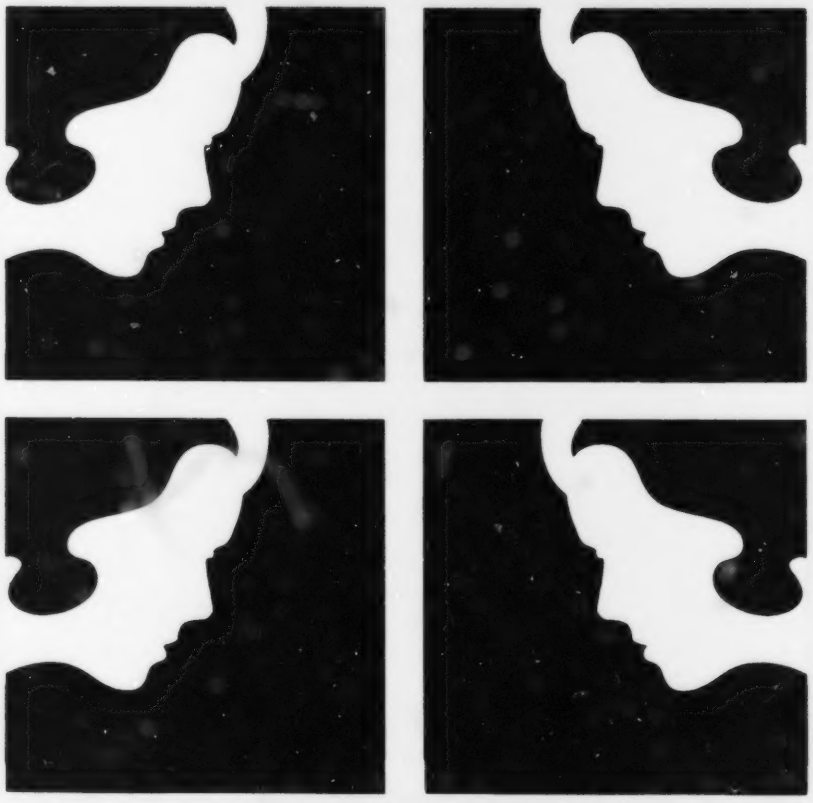
Report
1985

ORAL CONTRACEPTIVES



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REPORT ON ORAL CONTRACEPTIVES, 1985 BY THE SPECIAL ADVISORY COMMITTEE ON REPRODUCTIVE PHYSIOLOGY TO THE HEALTH PROTECTION BRANCH HEALTH AND WELFARE CANADA

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INTRODUCTION

Oral contraception remains the most popular and most reliable method of preventing pregnancy. However, problems associated with its use, in particular the occurrence of serious adverse effects, have prompted Health and Welfare Canada to distribute several reports on oral contraceptives to health professionals in this country since 1970. Major reports were prepared by the Special Advisory Committee on Reproductive Physiology to the Health Protection Branch in 1970[1] and 1975.[2] An updating by the committee of the latter document was distributed in 1978.[3]

The present report provides a current review of contraceptive technology in addition to providing some historical background on the use of oral contraceptives. Some material that is relevant to modern practice has been reproduced from the earlier reports.

It is important to realize that, in this document, we are discussing specifically contraception. On the other hand, the benefits and risks of oral contraceptives must be considered individually by the physician and his or her patient. For example, these compounds may be used to treat dysfunctional uterine bleeding, endometriosis, acne and hirsutism, dysmenorrhea, benign breast disease, and as replacement therapy, etc. Thus the potential risks or benefits must be considered by the physician in these circumstances as being possibly of a different magnitude than those which apply to a healthy woman seeking only reliable birth control. In effect, as with most areas of medical practice, the physician's judgement must be the deciding factor.

In the introduction to the previous report on oral contraceptives (OCs),[3] the committee stressed the importance of the increasing trend towards using oral contraceptive preparations containing a daily dosage of 50 mcg of estrogen or less. From an examination of recent marketing data,[4] this trend has been confirmed. The committee now recommends products containing 30-35 mcg of estrogen for conception control. It is still too soon, however, to determine whether or not the prescribing of OCs containing less than 50 mcg will further reduce the number of adverse effects associated with their use.

Figure 1 shows that the majority of prescriptions by physicians for OCs have been for products containing a dosage of estrogen less than 50 mcg. Each year, approximately 3 million women visit their physicians to discuss contraceptive methods. OCs are mentioned 88% of the time (Table 1).[4] In a comparison of contraceptive methods used by Canadian and U.S. women, OCs were used by 44% and 33%, respectively, of those women who were using some form of contraception including sterilization (Table 2).

Included with this report is a document entitled "Guidelines for the Directions for Use of Estrogen-Progestogen Combination Oral Contraceptives" which was prepared by the Committee in co-operation with the Health Protection Branch. This document will form the basis of all information on the subject of OCs to the medical profession from the pharmaceutical industry. Also included with this report are the texts of a patient package insert and a supplementary information booklet for patients who are considering the use of OCs.

Figure 1. Distribution of prescriptions for estrogen-progestogen oral contraceptives, by estrogen content. Source: IMS (Canada)

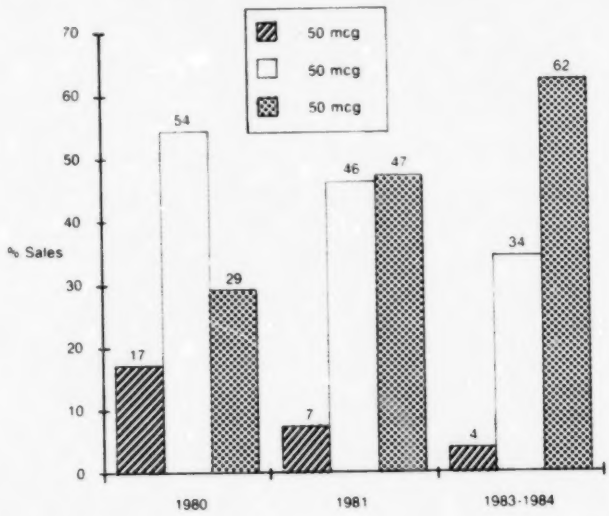


Table 1
Distribution of Contraceptive Mentions in Patient Visits to Physicians, by Type of Contraceptive Method Excluding Sterilization (Canada, 1984).4

Oral contraceptives	88%
Intra-uterine devices (IUDs)	9%
Vaginal creams, foams, gels	1.3%
Diaphragms	0.9%

In developing the information for patients, the parties worked under the conviction, as in the past, that it is the doctor and patient who must decide together whether or not OCs are to be used. However, the committee has found it necessary to depart from the philosophy that it is the sole responsibility of the doctor to inform the patient of the hazards of these products as he or she sees fit. Modern-day consumers are demanding more responsibility for their own health care. Women who are contemplating the use of OCs are increasingly requiring more information regarding the

Table 2
Comparison of Contraceptive Methods Used by Canadian and U.S. Women

	Canada	US
% Married women using some form of contraception	68%[a]	68%[a]
% All contraceptors, using:		
OCs	44%[b]	33%[b]
IUDs	8%[b]	9%[b]
condoms	8%[b]	11%[b]
periodic abstinence	5%[b]	5%[b]
sterilization	26%[c]	28%[d]

[a]*Source: 1978; Canadian Advisory Council on the Status of Women.*
[b]*Source: for US, married women only; for Canada, all women, 1976 data; Population Reports Series A, no. 6; Series B, no. 4; Series H, no. 6, all 1982; Series I, no. 3, 1981.*
[c]*Source: 1977; Report to the Committee on Abortion.*
[d]*Source: Married women of reproductive age, 1981 report of the Population Reference Bureau, titled "Patterns of Contraceptive Use Around the World."*

mechanism of action, benefits, and risks of oral contraception. These developments have been prompted in part by articles appearing in the popular press, and by discussions in the electronic media, of adverse effects associated with the use of OCs. Many of these articles, regrettably, have been highly sensationalistic and have served to dissuade many women, even young, healthy women for whom oral contraception is the ideal method of birth control, from using OCs. In addition, arising from the proceedings of legal actions taken in this country, recommendations have been made that women should be informed of the material risks of taking OCs, not just the symptoms of adverse effects that must be watched for during their use. As noted in the patient information and in the body of this report, new information is coming to light on non-contraceptive benefits of the pill. Taken into perspective with the most recent knowledge of the risks of taking OCs, a young, healthy woman should not be discouraged from their use.

The Patient Package Insert (PPI) is similar in format to that which has been used in the past. However, the material risks associated with OC use have been mentioned by name rather than only listing symptoms which must be watched for, as was the case previously. Conditions for which the use of OCs are contra-indicated are included. A few other changes also have been made. The PPI is to be dispensed with all packages of oral contraceptives.

The Supplementary Information Booklet was designed as an educational piece for all women who are contemplating the choice of a method of birth control. It contains that information in the PPI but includes more details of the benefits and risks of OCs as well as some discussion of the effectiveness and risks of other methods of contraception. It is intended to be read by the patient and discussed with her physician before she starts using OCs. Copies of these booklets will be made available to physicians and pharmacists by the manufacturers of OCs. A schema which illustrates the distribution of patient information on OCs is presented in Figure 2.

Figure 2. Dissemination of Information on Oral Contraceptives to Patients.

PATIENT

- will have discussed contents of Supplementary Information Booklet with physician before receiving first prescription for OCs.
- will receive First Prescription Package consisting of OCs, the Patient Package Insert, and the Supplementary Information Booklet from pharmacist with first prescription.
- will receive the Patient Package Insert (plus Booklet if replacement needed) with all subsequent prescriptions.

PHARMACIST

- for the initial prescription for OCs for a patient will dispense a First Prescription Package consisting of OCs, the Patient Package Insert, and the Supplementary Information Booklet.
- will offer the booklet to the patient with prescription refills in the event the original booklet was misplaced.

PHYSICIAN

- in possession of Report on OCs, 1985; CPS 1985; and copies of Supplementary Information Booklets from manufacturers.
- will discuss context of Supplementary Information Booklet with patient prior to prescribing OCs.

MANUFACTURER

- will ensure that pharmacists receiving quantities of OC packages will have adequate supplies of First Prescription Packages plus extra Supplementary Information Booklets for distribution with prescription refills as required.
- will ensure availability of Supplementary Information Booklets to physicians by:
  (a) messages in advertisements that copies are available from company representatives,
  (b) distribution to physicians by company representatives.

NEW INFORMATION CONCERNING ORAL CONTRACEPTIVES

New Lower Dose Preparations

New concepts of oral contraception which have been recently introduced provide for combinations of estrogen-progestogen with a reduction in the total monthly dosage of progestogen. These products may result in a decrease in intra-menstrual bleeding and withdrawal amenorrhea without adversely affecting contraceptive efficiency and may reduce the incidence of adverse effects (see the section on SELECTION OF THE ORAL CONTRACEPTIVE).

Beneficial Effects

In this report the committee has incorporated new information, in many areas more reassuring to the user of the contraceptive pill. Evidence has appeared that oral contraception is associated with the following beneficial effects:[5]

1. It is the most effective method of reversible contraception available.
2. In most cases, it eliminates dysmenorrhea.
3. It reduces menstrually-related anemia.
4. It reduces the risk of endometrial carcinoma.
5. It appears to reduce the incidence of benign breast lesions.
6. It reduces the incidence of pelvic inflammatory disease.
7. It appears to reduce the incidence of ovarian cysts and ovarian cancer.
8. It reduces the incidence of ectopic pregnancy.
9. It may reduce the incidence of rheumatoid arthritis.

Reduced Hospitalization Rates

Reduced hospitalization rates for a number of clinical conditions recently have been demonstrated.[6] These are shown in Figure 3. The figures are for the U.S.A., 1982.

The use of OCs also prevents a number of diseases that usually do not require hospitalization. For example, in the U.S.A. an estimated 44 400 non-hospitalized cases of pelvic inflammatory disease are averted annually, as are approximately 3200 cases of rheumatoid arthritis and 32 000 cases of iron-deficiency anemia.[6]

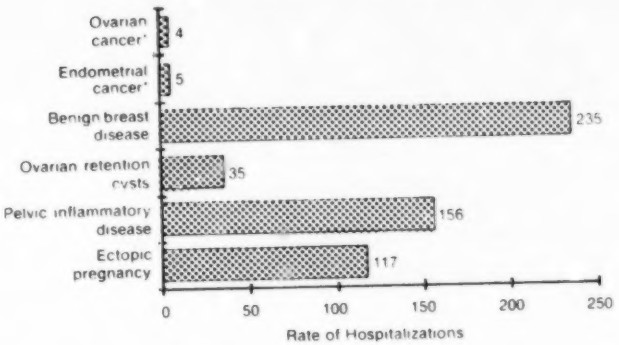
Since the previous report,[3] the following changes in our knowledge of OCs have become apparent from the medical literature.

1. **Recent Observations Regarding Circulatory System Complications in Oral Contraceptive Users[7]**

   (a) Adverse effects are not correlated with duration of use.

   (b) Adverse effects are increased in non-smoking women over the age of 35 years.

Figure 3. Estimated annual rate of hospitalizations prevented by use of oral contraceptives per 100 000 pill users (USA)



*Based on ever-users aged 20-54

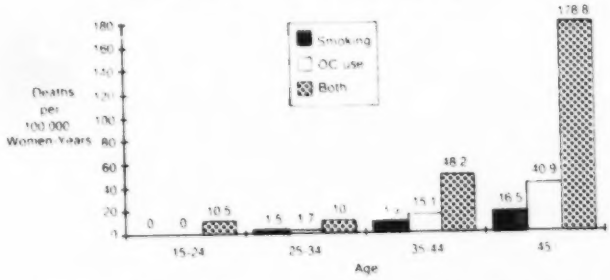
Adapted with permission from Making Choices: Evaluating the Health Risks and Benefits of Birth Control Methods, by Howard W. Ory, M.D., Jacqueline D. Forrest, Ph.D., and Richard Lincoln. The Alan Guttmacher Institute, New York, 1983.

   (c) Adverse effects are increased in all women who smoke in excess of 15 cigarettes per day, especially in those who are over 35 years of age.

   (d) There is an apparent association between cardiovascular adverse effects and increasing parity, especially in women who smoke even though they may be currently not using OCs.

The rates of excess mortality from circulatory system disease among women enrolled in the Royal College of General Practitioners Oral Contraceptive Study[8] are shown in Figure 4.

Figure 4. Rates of excess circulatory system disease mortality in the Royal College of General Practitioners Oral Contraception Study attributable to smoking, ever-use of oral contraceptives, or both, by age



Note: Rates shown are excess over rates in non-smoking women not using OCs.

Source: Population Reports, Series A, Number 6, May-June 1982. Adapted from Royal College of General Practitioners. Further analysis of mortality in oral contraceptive users. Lancet 1(8219): 541-546. March 7, 1981.

2. The Progestogen-Estrogen Potency Controversy

For many years, it was felt that only the estrogen content in OCs was responsible for both venous thromboembolic and arterial complications. However, this is no longer the case. More recent information has linked the synthetic progestogens to hypertension, arterial complications, and a reduction of high density lipoprotein (HDL) cholesterol. On the other hand, estrogen tends to raise total cholesterol and triglycerides but, at least theoretically, acts in a protective fashion against arterial complications because it increases HDL cholesterol.

Controversy exists concerning the relationship between "potency" and dosage when selecting an estrogen-progestogen combination OC. There are only 2 estrogenic steroids currently used in OCs — mestranol, and its metabolite ethinyl estradiol. These 2 estrogens are of approximately equal potency when used as single agents. However, there are 3 different classes of progestogens (pregnanes, e.g. medroxyprogesterone, estranes, e.g. norethindrone, and gonanes, e.g. norgestrel). Most progestogens in OCs are found in the estrane category. These 3 classes all have different biological activities when used alone. Therefore, comparison of potency or clinical effects, even when used as a single agent in an identical dose, is impossible.

There is no currently available method for comparing the various progestogenic compounds when they are combined with varying dosages of either of the 2 estrogens. Comparisons of potency based upon the delay of menses tests of Greenblatt[9] or Swyer[10] are not feasible because of the many variables. Current articles supporting the use of one or other combination OC based upon such potency studies are not accepted as scientifically valid by the committee. In a recent publication, Swyer[11] has reviewed the many problems inherent in comparisons of progestogen potency. He has noted that the metabolic actions of progestogens which are, or are potentially, toxic are a far more important consideration than the mere potency ratio. At this time, however, there is no statistically sound evidence that OCs of differing progestogenic content are deleterious or advantageous when side effects among the various brands are compared.

The committee reaffirms its opinion that, in selecting an OC, the least progestogenic and estrogenic effects, consistent with effectiveness and good cycle control, should be the goal. The committee recommends an estrogenic content of between 30 mcg and 35 mcg. With regard to the type or dosage of a progestogen in combination with the estrogen, clinical judgment as applied to specific patient groups will be a more suitable guide than relying upon suggested dosages, potencies, or implied benefits or side effects of various progestogens.

3. Breastfeeding and Post-partum Contraception

Recent publications from the American College of Obstetricians and Gynecologists,[12] and the American Academy of Pediatrics[13] have suggested that the use of OCs during the lactation period is acceptable. In the section on Resuming Oral Contraception After Parturition or Abortion, specific recommendations for the post-partum use of OCs are given.

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HORMONAL METHODS OF CONTRACEPTION

It is well-established that OCs containing estrogen and progestogen affect hypothalamic, pituitary and ovarian function. They may alter many other physiological systems. Although the exact mechanisms of action are incompletely understood, there is universal agreement that the inhibition of the "ovulatory peak" of luteinizing hormone (LH) is a constant and contributing factor. OCs may exert their contraceptive action in at least 4 ways.

1. Alteration of the physical and chemical properties of the cervical mucus, thereby inhibiting sperm penetration.
2. Endometrial changes hindering implantation.
3. Inhibition of ovulation.
4. Subtle changes in the hypothalamic-pituitary-ovarian axis with possible altered corpus luteum function. The steroid profiles quite often indicate either an absence of or insufficient luteal activity, or a significant and gradual decrease in several of the indices of luteal function.

Probably none of these factors alone accounts for the high degree of anti-fertility effect of any OC. They may all play a part in the production of effective contraception.

OCs were developed to prevent unwanted pregnancies. The first generation of OCs contained norethynodrel or norethindrone. Their efficacy was related to suppression of ovulation which was attributed primarily to these progestogens. To decrease cost and adverse effects, investigators and drug companies reduced the amount of progestogen. Eckstein et al[1] and Mears[2] reported studies with OCs containing 2.5 mg of norethynodrel and 36 mcg of mestranol. The efficacy of this combination as a contraceptive dropped from 100% to 71%. This emphasized the fact that suppression of ovulation was related not only to progestogens but also to estrogens and to the ratio between both compounds. Eckstein suggested that when the dosage of norethynodrel is lowered, the concentration of estrogen becomes critical; and that further reduction of the dosage of estrogen impairs the contraceptive efficacy of these preparations.

Combination Oral Contraceptives

Following this work, a new generation of combination products containing a lower dosage of a progestogen and a higher concentration of estrogen passed clinical trials with honors. Taken properly, these new combinations containing the estrogens ethinyl estradiol or mestranol and the progestogens norethindrone, norethindrone acetate, norethynodrel, ethynodiol diacetate, or dl-norgestrel (or levonorgestrel) have been found to be almost 100% effective in preventing pregnancy, even when the estrogen dosage is 30-35 mcg. Because the possibility of developing thromboembolism is believed to be related most often to an estrogen dosage higher than 50 mcg, it is generally agreed that 30-35 mcg of an appropriate estrogen is the optimal dosage which is compatible with patient compliance, efficacy, and few risks of thromboembolism and minor side effects.

Sequential Oral Contraceptives

Sequential OCs were also introduced on the market for a short while. The well-known ability of estrogen to suppress ovulation was used in association with a progestogen in the latter part of the cycle. Their main disadvantage was that they required a higher dosage of estrogen to be efficacious, and even then their efficacy was lower than that of the combination type although higher than other available methods of contraception. The sequential OCs were withdrawn from the Canadian market early in 1976 following a review of data by a task force of this committee which suggested that these products infrequently led to the development of endometrial carcinoma.

Continuous Low Dosage Progestogens (The Minipill)

Oral contraceptive preparations containing progestogen only (minipills) were introduced on the market in the early 1970s. Elimination of the estrogen altered the mode of action and consequently lowered the efficacy. There is a wide variation in the pregnancy rates for compounds that have been studied. For the product that is available in Canada, which contains norethindrone, the pregnancy rate is approximately 1.0 to 2.0 per 100 women-years. This compound is indicated mostly for a limited patient population in which the use of estrogen or a higher dosage of progestogen would be undesirable. The main problem associated with the use of continuous low dosage progestogens as contraceptive agents is the high incidence of poor cycle control resulting in unpredictable bleeding. Because of the possibility of missed organic disease, serious consideration should be given to discontinuing this medication if bleeding persists.

Biphasic and Triphasic Oral Contraceptives

During the early 1980s, probably the most important development in oral contraceptive practice has been the introduction of biphasic and triphasic combined formulations. In triphasics, the dosage of the progestogen is increased on two occasions from an initial low amount during the treatment cycle. The dosage of estrogen also may be increased during mid-cycle. The resultant changes in the estrogen to progestogen ratio are compatible with a low incidence of intra-menstrual bleeding, good tolerance, cycle control and good efficacy. In both biphasic and triphasic combined formulations, the total amount of progestogen ingested in the cycle has been reduced. Because hypertension, alternations in carbohydrate and lipid metabolism, and other events have been attributed to

the total quantity of progestogen, a reduction in the total monthly intake of progestogen should have a beneficial effect.

Injectable Progestogens

An injectable contraceptive such as medroxyprogesterone acetate has its own special characteristics. The absence of estrogenic and androgenic activities is an advantage for women in whom estrogens (as in OCs) are contra-indicated but who desire a highly effective contraceptive method. Medroxyprogesterone acetate has fewer known risks of serious adverse reactions than have the other highly effective methods of contraception. The estimated mortality rate for medroxyprogesterone acetate is lower than that estimated for intra-uterine devices, OCs or childbirth. In addition, this method requires an injection every 3 months which permits close contact with health care providers and presents other advantages such as reductions in menstrual bleeding with its associated discomforts, premenstrual tension, cramping, bloating and iron deficiency anemia.

Pregnancy rates have been comparable to those reported for OCs, ranging from 0.0 to 1.2 per 100 women-years, using a 150 mg medroxyprogesterone acetate administration every 90 days.[3-6]

Medroxyprogesterone acetate may be advantageous for use in those individuals:

— with a high risk of infection from IUDs,

— who smoke, especially if over the age of 35,

— at risk of cardiovascular problems, regardless of age and smoking habits,

— who have had repeated failures when using other methods,

— for whom amenorrhea would provide relief from dysmenorrhea or premenstrual syndrome,

— for whom amenorrhea provides a hygienic or medical advantage,

— who cannot tolerate the side effects of estrogens, and

— who are perimenopausal.

However, more frequent side effects such as menstrual disturbance, weight gain, headache, and a delay in the return of fertility may render the use of medroxyprogesterone acetate less desirable for certain patients.[7]

The use of depot medroxyprogesterone acetate has been discussed previously by the committee.[8]

Implants

The development of this new contraceptive method began in 1966 and clinical studies have been in progress since 1968. One type of implant consists of silicone rubber capsules of small diameter (2.4 mm) placed under the skin of the upper arm. These capsules contain levonorgestrel and provide truly long-term protection from pregnancy for at least 5 years.

The pregnancy rate has been 0.5 per 100 women-years over the entire 5-year period of recommended use.[9,10] At any time, the implants can be placed and removed involving minor office surgery. After removal, normal fertility is rapidly restored. Upon placement, diffusion of levonorgestrel from the capsules begins immediately and contraceptive effectiveness starts at once. The high level of effectiveness is related to alterations of the cervical mucus, which is rendered highly impenetrable to sperm.

Menstrual disturbances are the most frequent complaint of users. In the first year of use, they are the main reason for discontinuing the use of implants (2.2-8.3%). These disturbances are observed less frequently in subsequent years of use. The silastic implant technique, being a progestogen-only method, eliminates the risks associated with estrogens. The constant, low-level release of progestogen from implants is an advantage over the high blood levels of progestogen reaching the liver and other organs, as characteristic of OCs.

Looking to the Future

Implants and vaginal inserts have been developed in other forms such as rods, rings, capsules and microspheres, and other progestogens such as norethindrone have been incorporated in these.[11-13] None of the injectables, implants or other methods are as yet approved for marketing in Canada. It is likely, however, that some of these will become available in the near future.

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NON-HORMONAL METHODS OF CONTRACEPTION

The rates of failure of the methods listed below are based upon Pearl's formula (see Appendix I) and are, therefore, subject to the limitations of this method of calculation. The calculated rate of pregnancy without protection is about 80 per 100 women-years of exposure. The wide ranges in rates of pregnancy that have been reported for the various contraceptive methods[1] are shown in the Supplementary Information Booklet for patients.

Post-coital Douches

The post-coital douche reduces the chances of conception only slightly. It is by far the least effective method of contraception.

The Rhythm Method and Natural Methods

The pregnancy rate for the rhythm method, possibly because of irregular cycles and careless timing, is 25 to 35 per 100 women-years. However, a much lower rate can be achieved if the method is correctly taught, understood, and consistently practised or used in conjunction with measurements of basal body temperature.

Coitus Interruptus

Coitus interruptus, the practice of which is still widespread, has an effectiveness that has been traditionally underestimated by the medical profession. The accepted pregnancy rate is 25 per 100 women-years of exposure.

Spermicides

Spermicides such as jellies, creams and foams are more effective if they are used together with a vaginal diaphragm or condom. The pregnancy rate for spermicides alone is 25 to 30 per 100 women-years of exposure. The effectiveness of spermicides when used alone is low because patient motivation varies and instructions for use may be improperly followed. Factors that seem to affect efficacy include failure to insert the spermicide high enough into the vagina to cover the cervix, failure to apply the product before each coital act, and failure to wait until the spermicide is totally dispersed before coitus begins.

There is no conclusive evidence that spermicides cause congenital malformations in the event of pregnancy following their use.

Vaginal Diaphragms

If used properly and consistently, the diaphragm offers a level of protection reflected by a failure rate of 15 to 18 pregnancies per 100 women-years of exposure. In clinical practice, this pregnancy rate is obtained with the diaphragm together with a spermicidal cream or jelly. Higher rates have been reported for populations unaccustomed to this method.

Condoms

Due to the escape of semen from a possible break or tear, the use of the condom is associated with a pregnancy rate of 4 to 15 per 100 women-years of exposure.

Intrauterine Contraceptive Devices (IUDs)

According to the World Health Organization's Special Programme of Research in Human Reproduction, failure rates for the most widely used types of IUDs are in the order of 0.5 to 3.7 pregnancies per 100 women during the first year.[2] Lower rates occur during subsequent years. These IUDs may incorporate either copper or a progestogen to potentiate effectiveness.

IUDs are best suited for those populations unaccustomed to the consistent practice of contraception or for couples who find other methods less acceptable. Case-control and other studies[3,4] have confirmed an association between IUD usage and the risk of pelvic inflammatory disease (PID). The age-adjusted relative risk of PID was 8.6 with 95% confidence limits of 5.3 and 13.8. The risk is lowest for progesterone- or norgestrel-releasing IUDs and highest for inert IUDs. For these reasons, there is a consensus that caution should be used in inserting IUDs into the nulliparous woman. The device should be inserted only after the risks have been explained to the patient.

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POST-COITAL INTERCEPTION

Post-coital interception (also called post-coital contraception) remains a new but incompletely understood therapy.[1] There is evidence that the administration of estrogen, progestogen, or estrogen-progestogen combinations within 72 hours of unprotected intercourse may have a definite interceptive effect. The limitations of this approach must be understood clearly. It is satisfactory only for an emergency situation where unprotected intercourse has occurred unexpectedly, and where the medication can be given within 72 hours of exposure. **The high-dose estrogen-only interceptive regimens are no longer recommended** because, in the event of a method failure, the risks of teratogenic effects and malignant disease in the offspring of women exposed to diethylstilbestrol (DES) during pregnancy are unacceptable.[2]

Newer approaches to post-coital interception are being used. They stand out in their simplicity, efficacy and acceptability.[3] In one of these regimens, women are treated with dl-norgestrel (0.5 mg), and ethinyl estradiol (50 mcg) 2 tablets per dose taken on 2 occasions 12 hours apart within 72 hours of an unprotected coital exposure.[3] A failure rate of 1.6% has been reported.[4]

The interceptive effect of the combination of dl-norgestrel and ethinyl estradiol is related to a variable luteal phase dysfunction (luteolytic), out-of-phase endometrial development, and disordered tubal transport of the fertilized ovum.[5]

The insertion of copper-containing IUDs has been effective for post-coital interception.[6] This serves the added purpose of providing continuing fertility control. However, IUDs should not be inserted in this situation in women who have multiple sexual partners, who have been raped, or who have a recent history of pelvic inflammatory disease. **Also, as previously discussed, IUDs are not usually suitable for the nulliparous woman.**

Other methods currently are being investigated for safety and efficacy.[7-9]

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PATIENT SELECTION

OCs are the safest and most efficient reversible method of birth control when used by well-motivated women who have no evidence of conditions that preclude their use or effectiveness. Patient selection cannot be stated simply. It requires a dialogue between patient and physician. The physician needs information concerning the patient's physical and mental health, family and personal history, and the woman's needs for protection against pregnancy. **At the initial visit, the patient should participate in a full discussion of the benefits and risks of oral contraception as well as of other contraceptive methods so that when the decision to use an OC is made, she will feel that she has selected the best method for her.** The time spent on preliminary counselling is reflected in an increase in patient compliance.

The majority of women deciding to use OCs will be young and healthy, and have no evidence of conditions that preclude their use. The history should include all obstetrical and gynecological information with special emphasis on estrogen-dependent malignancies, diabetes, thromboembolic disorders, depressive reactions, hypertension, classical migraine headaches and jaundice.

Well-recognized contra-indications to the use of OCs exist as follows:

1. Thrombophlebitis, thromboembolic disorders, or a history of these conditions.
2. Cerebrovascular disorders.
3. Myocardial infarction.
4. Active liver disease.
5. History of cholestatic jaundice.
6. Known or suspected carcinoma of the breast.
7. Known or suspected estrogen-dependent neoplasia.
8. Undiagnosed abnormal vaginal bleeding.
9. Any ocular lesion arising from ophthalmic vascular disease such as partial or complete loss of vision or defect in visual fields.
10. When pregnancy is suspected or diagnosed.

PHYSICAL EXAMINATION

Before OCs are used, a thorough physical examination should be made including a blood pressure determination and examination of the breasts, liver, extremities and pelvic organs. A Papanicolaou smear should be taken for all patients who have had sexual intercourse. A urinalysis is required.

SELECTION OF THE ORAL CONTRACEPTIVE

Physicians should choose an OC which is nearly 100% effective yet possesses the greatest safety margin in terms of serious side effects. The committee recommends a starting daily dosage of estrogen of 30-35 mcg, which may be later increased, if necessary, to maintain good cycle control. The practitioner may make such a choice from the list of currently available preparations shown in Table 3. At present, the triphasic preparations probably fit best into this description, i.e. that combination with the lowest effective dose of estrogen and progestogen.

The lower dose estrogen-progestogen combination OCs have a higher incidence of breakthrough bleeding (**BTB**) and spotting during the first few months of use. The patient should be informed of this. She should be assured that BTB and spotting are not serious adverse effects and she should be encouraged to continue using the OC at least until the time of the first follow-up visit at 3 months.

For the average, healthy, young woman starting oral contraception, an OC containing an average daily dose of 30-35 mcg of estrogen is strongly recommended. There is relatively little difference, clinically, between the 2 estrogens available in OCs on the Canadian market. With respect to progestogens, however, there are 5 different ones contained in the many OCs currently available. For any given progestogen, it is suggested that the lowest dosage is preferable if this is consistent with good cycle control. Certainly, in some patients, it will be necessary to increase the dosage of estrogen to 50 mcg in order to maintain adequate cycle control. However, doses of estrogen in excess of 50 mcg should be used sparingly and only in special circumstances.

To reiterate, the lowest dosages of **both** ingredients that are consistent with the desired biological effects are the safest and best for your patient. The following points should be kept in mind:

1. The recommended dosage of estrogen for contraception is 30-35 mcg. Use the lowest dosage of any given progestogen that will provide for contraception and good cycle control.
2. OCs containing 50 mcg of estrogen should be used only when good cycle control cannot be attained with compounds containing 30-35 mcg of estrogen. Varying the dosage of the progestogen may aid in achieving good cycle control.
3. OCs containing less than 30 mcg of estrogen may be associated with a higher incidence of breakthrough bleeding and spotting than that for the products containing 30 mcg or more of estrogen.
4. The use of estrogen-progestogen combinations containing a daily dosage of estrogen in excess of 50 mcg is not acceptable for contraception. These products may be given for other medical purposes and contraception may be an added benefit.

Table 3
Oral Contraceptives Available in Canada[1]

Product	Manufacturer	Estrogen	mcg/ Tablet	Progestogen	mcg/ Tablet
20, 30 & 35 mcg Estrogen			(days in brackets for biphasics & triphasics)		
Minestrin 1/20	Parke-Davis	Ethinyl Estradiol	20	Norethindrone Acetate	1000
Min-Ovral	Wyeth	Ethinyl Estradiol	30	d-Norgestrel[2]	150
Loestrin 1.5/30	Parke-Davis	Ethinyl Estradiol	30	Norethindrone Acetate	1500
Demulen 30	Searle	Ethinyl Estradiol	30	Ethynodiol Diacetate	2000
Ortho 1/35	Ortho	Ethinyl Estradiol	35	Norethindrone	1000
Ortho 0.5/35	Ortho	Ethinyl Estradiol	35	Norethindrone	500
Brevicon 0.5/35	Syntex	Ethinyl Estradiol	35	Norethindrone	500
Brevicon 1/35	Syntex	Ethinyl Estradiol	35	Norethindrone	1000
Ortho 10/11[3,5]	Ortho	Ethinyl Estradiol	35(21)	Norethindrone	500(10) 1000(11)
Ortho 7/7/7[4,5]	Ortho	Ethinyl Estradiol	35(21)	Norethindrone	500(7) 750(7) 1000(7)
Triphasil[4,5]	Wyeth	Ethinyl Estradiol	30(6) 40(5) 30(10)	d-Norgestrel[2]	50(6) 75(5) 125(10)

Table 3 (concluded)

Product	Manufacturer	Estrogen	mcg/ Tablet	Progestogen	mcg/ Tablet
50 mcg Estrogen — For conception control only when lower dosage estrogen formulations prove to be unsatisfactory.					
Ovral	Wyeth	Ethinyl Estradiol	50	d-Norgestrel[2]	250
Norlestrin 1/50	Parke-Davis	Ethinyl Estradiol	50	Norethindrone Acetate	1000
Norlestrin 2.5/50	Parke-Davis	Ethinyl Estradiol	50	Norethindrone Acetate	2500
Demulen 50	Searle	Ethinyl Estradiol	50	Ethynodiol Diacetate	1000
Ortho-Novum 1/50	Ortho	Mestranol	50	Norethindrone	1000
Norinyl 1/50	Syntex	Mestranol	50	Norethindrone	1000
75 & 80 mcg Estrogen — Should not be used for conception control.					
Enovid 5	Searle	Mestranol	75	Norethynodrel	5000
Ortho-Novum 5	Ortho	Mestranol	75	Norethindrone	5000
Ortho-Novum 1/80	Ortho	Mestranol	80	Norethindrone	1000
Norinyl 1/80	Syntex	Mestranol	80	Norethindrone	1000
100 mcg Estrogen — Should not be used for conception control.					
Norinyl-2	Syntex	Mestranol	100	Norethindrone	2000
Enovid-E	Searle	Mestranol	100	Norethynodrel	2500
Ovulen 1	Searle	Mestranol	100	Ethynodiol Diacetate	1000
Ovulen 0.5	Searle	Mestranol	100	Ethynodiol Diacetate	500
Ortho-Novum 0.5	Ortho	Mestranol	100	Norethindrone	500
Ortho-Novum 2	Ortho	Mestranol	100	Norethindrone	2000
Estrogen Free					
Micronor	Ortho			Norethindrone	350

[1] *Most of the estrogen-progestogen combination products listed in this table are also available with inert tablets that permit uninterrupted 28-day cycles of therapy.*

[2] *Supplied as the dl-racemate in double the amount shown.*

[3] *Biphasic product.*

[4] *Triphasic product.*

[5] *The number of days each dosage of estrogen and progestogen is to be taken is shown in brackets in the dosage columns.*

FOLLOW-UP AND DURATION OF USE

The first follow-up examination should be done at 3 months. Thereafter, examinations should be done at least every 6 months if the patient is a teenager, and at least annually for others. At each annual visit, examinations should include those procedures outlined above that were done at the initial visit.

If annual clinical review justifies it, the medication may be continued. In healthy young women who are menstruating normally before taking OCs, the risk factors tend to be at a minimum and continuous contraception should not be interrupted. The practice of giving the patient a "rest" for some months after several years of OC use is unnecessary and may lead to an increased incidence of unwanted pregnancies. OCs may be prescribed until the woman reaches the age of 35 (in the absence of untoward effects). After this age, alternate methods of contraception should be considered. The problems associated with smoking, parity and age are discussed in the following sections.

SPECIFIC PROBLEMS ASSOCIATED WITH CONTRACEPTIVE USE

1. CONTRACEPTION IN TEENAGERS

Teenagers present a special problem. They are sporadic rather than consistent contraceptive users. The committee recommends that OCs may be prescribed, but teenagers should have full information on other contraceptives such as vaginal creams, foams and inserts; the diaphragm and condom; and the "morning-after pill"; most of which are more easily obtainable on short notice. Those teenagers who are contemplating or are already engaged in sexual activity must be offered protection against the greater risk of pregnancy. There is no evidence, at present, that OCs are contra-indicated in these young women. The adverse consequences of an unwanted pregnancy in a young girl under the age of 17 far outweigh any physiological effects associated with inhibition of gonadotropin production by OCs. There is no contra-indication **to continuing** on the oral contraceptive pill, as long as the girl is sexually active. As for adults, there is no indication **for discontinuing** the use of OCs for a "rest" as has been the practice in some areas. The only result is an increased incidence of unwanted pregnancy. To enhance patient compliance, teenagers should be seen at 6-month intervals.

2. CONTRACEPTION IN WOMEN OVER THIRTY-FIVE

There is probably more anxiety in women over the age of 35 about getting pregnant than in women of almost any other age. This is very understandable and often leads to the question of when the woman should discontinue contraception, as she may be near or at the menopause. Fertility decreases with age, particularly in the late thirties, but there have been many reports of pregnancies in the forties and even early fifties. As long as the patient is menstruating, even irregularly, she may become pregnant. Therefore, she should continue to use a method of contraception. It is probably safe to allow a patient to discontinue using her contraceptive 1 year after the clinical onset of the menopause or 6 months following 2 gonadotropin estimations 3 months apart, both showing menopausal levels of FSH and LH.

Most women who are over the age of 35 will be using a contraceptive method to which they have become accustomed and which they have used successfully. Some married couples in this age-group still use the condom, and there is no need to change. As a result of unfavorable discussions of the oral contraceptive pill by the media, more and more women in this age group will have been changed to a diaphragm or an IUD. Many couples will have chosen permanent contraception in the form of tubal ligation or vasectomy.

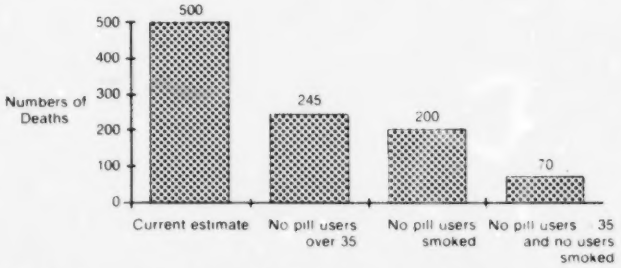
In summary then, a barrier method, a prolonged-action IUD, sterilization in the woman, or vasectomy in the partner are probably the best routes to safe contraception in the age-group of 35 years or more.

3. ORAL CONTRACEPTIVES AND SMOKING

"Given the age distribution and distribution of smokers among pill users in 1982, it can be calculated that ....an estimated 86% of deaths associated with oral contraceptive use result from the combination of pill use and smoking and from reliance on the pill by women aged 35 and older. About 4 in 10 pill users smoke, and about 6% are 35-44 years old. The approximately 500 deaths (U.S.A.) attributable to pill use each year could be reduced to about 70 if no pill users smoked and none took the pill after her 35th birthday. If no pill users smoked, the estimated number of deaths attributable to pill use would be reduced to about 200 per year."[1]

These figures are shown graphically in Figure 5.

Figure 5. Estimated annual number of pill-related deaths (USA), and projected number that would occur if no one took the pill who was over age 35, no pill users smoked, and no one took the pill who was over age 35 and no pill users smoked.



Adapted with permission from Making Choices: Evaluating the Health Risks and Benefits of Birth Control Methods, by Howard W. Ory, M.D., Jacqueline D. Forrest, Ph.D., and Richard Lincoln. The Alan Guttmacher Institute, New York, 1983.

Heavy smoking (more than 15 cigarettes per day) appears to be a very significant risk factor in the development of vascular disease in users of OCs.

An increased incidence of myocardial infarction, stroke, and arterial thromboembolism has been observed in several studies.[2,3]

The risk of myocardial infarction in OC users increases with the number of cigarettes smoked per day.[3]

Mortality rates per 100 000 women who smoked were 10.2 in OC users vs 2.6 in non-users in the 30- to 39-year age-group, and in those over 40 who also smoked, the rates were 62.0 in users compared to 15.9 in non-users.[4]

Smoking also increases the relative risk of hemorrhagic stroke. OCs increase this risk to 1.2 in non-smokers, whereas heavy smokers who are also OC users have a relative risk of 6.1 to 7.6.[5]

Overall, heavy smoking potentiates the risk of major types of vascular disease. Indeed, it appears to be the **most significant risk factor.** When combined with one or more of the other risk factors such as hypertension, increasing age over 30 years, diabetes, obesity and hyperlipoproteinemia, smoking has a very significant synergistic effect.

It is recommended that women should be counselled to stop smoking if they wish to use OCs.

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4. RESUMING ORAL CONTRACEPTION AFTER PARTURITION OR ABORTION

After the delivery of a baby, non-nursing patients can expect menstruation to resume at about 6 weeks. Therefore, OCs may be given 4 weeks after the date of delivery. OC-enhanced thrombotic episodes are minimal at this time.

A recent study has shown that in normal breast-feeding mothers, ovulation recommences approximately 5 months after delivery.[1] If the patient is breast-feeding, low dosage OCs do not interfere with continuation of lactation.[2,3] The hormones contained in these products are excreted in the breast milk in small quantities, but do not alter its quality or volume if they are not given before 4 to 6 weeks after delivery.[4] The long-term effects of the small amount of hormones transmitted to the neonate are not known. Therefore, both the benefits and possible risks of OCs must be considered by the patient and her physician and these should be weighed against the benefits and risks of alternate methods of contraception.

For patients who wish to start using OCs after a first trimester abortion, the menstrual cycles may be expected to return after 4 weeks. OCs, therefore, may be given immediately after the abortion is complete. Following a mid-trimester abortion, menstruation is not expected before 6 weeks. OCs may be given 2 weeks after the abortion, by which time coagulation mechanisms should have returned to normal.

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5. ORAL CONTRACEPTIVES AND DRUG INTERACTIONS[1,6]

It is well-known that OCs induce a number of changes in the metabolic equilibrium. As a result, the pharmacological action of drugs used concurrently with OCs may be enhanced or antagonized. In some instances, it may be necessary to withdraw OCs in order to adequately treat a particular disease. In other cases, the dosage of concomitant medication may need to be reduced or increased.

Conversely, certain drugs that induce intracellular enzymes may augment the metabolic degradation of estrogenic and progestogenic components of OCs and thereby reduce their efficacy. Phenobarbital and other anticonvulsant drugs such as carbamazepine, phenytoin and primidone act in this manner. So does rifampicin. Anticonvulsants also have been associated with an increase in sex-hormone-binding globulin (SHBG) which may reduce the amount of free-circulating hormones and reduce the effectiveness of OCs. Other drugs such as ampicillin and tetracycline may influence the absorption of OCs by modifying the intestinal flora and thereby interfering with the enterohepatic circulation of estrogen. Theoretically, this also would be true for other anti-microbials that have a significant effect upon the intestinal flora.

Inhibition of hepatic microsomal enzymes by certain drugs can result in impaired degradation of OCs. Tricyclic antidepressants, ASA, allopurinol, chloramphenicol and other agents may be expected to potentiate the actions of OCs and increase the incidence or severity of adverse effects such as fluid retention, hypertension and thromboembolic disorders.

The interactions between OCs and other drugs which result in reduced contraceptive efficacy are more prominent today than in former years when OCs were given in relatively large dosages. With the advent of low-dosage preparations, the concomitant administration of OCs with other drugs has led to more frequent reporting of breakthrough bleeding and spotting and unintended pregnancies. The physician always should be mindful of the concurrent usage of any drug, including over-the-counter preparations the patient may be taking, in order that the woman may be advised properly of the best contraceptive method. The patient also should be informed of any possible drug interactions that may occur when other drugs are prescribed for her.

Breakthrough bleeding or spotting in an OC user who is taking other medication is suggestive of a reduced contraceptive efficacy. In patients who are receiving short courses of treatment with other drugs, the use of a supplementary method of contraception, such as a barrier method, during the period of therapy and for a short time thereafter, may be a wise precaution. This practice would depend upon whether or not the patient needs to avoid pregnancy as much as possible. The substitution of the patient's OC with a high dosage product may also correct the problem, but this approach is not recommended because of the increased risks of serious adverse effects inherent in the use of large dosages of contraceptive hormones. However, patients who require long-term therapy, e.g. with anticonvulsants, and who develop signs of reduced efficacy of OCs probably should be considered for alternate methods of contraception.

It is unfortunate that many interactions between OCs and other drugs are not well-documented in the literature. This is the consequence of a lack of clinical trials, which obviously would be unethical to conduct, wherein the degree of contraceptive failure due to drug interactions is studied. Presently known or suspected drug interactins are summarized in Tables 4, 5 and 6. These have been divided into interactions with drugs that may reduce the efficacy of OCs, drugs whose action may be modified by OCs, and drugs that may potentiate the adverse effects of OCs.

Table 4
Drugs That May Reduce the Efficacy of Oral Contraceptives

Therapeutic Agent	Mode of Action
Anticonvulsants:	
phenobarbital carbamazepine ethosuximide phenytoin primidone	Reduced efficacy of OCs occurs primarily due to induction of hepatic microsomal enzymes causing reduced circulating levels of contraceptive steroids. Also, increased levels of sex-hormone-binding globulin (SHBG) results in decreased free-circulating hormones.
Antibiotics:	
ampicillin penicillin	Altered intestinal flora and "intestinal hurry" (resulting in reduced enterohepatic circulation) have been implicated in reduced OC efficacy.
griseofulvin	Stimulation of hepatic metabolism of contraceptive steroids may occur.
chloramphenicol metronidazole neomycin nitrofurantoin sulfonamides tetracycline	Induction of hepatic microsomal enzymes. Also disturbance of enterohepatic circulation.
rifampicin	Increased metabolism of progestogens. Suspected acceleration of estrogen metabolism.
Sedatives and Hypnotics, Tranquilizers:	
benzodiazepines barbiturates chloral hydrate glutethimide meprobamate	Induction of hepatic microsomal enzymes.
Antacids	Decreased intestinal absorption of progestogens.
Other Drugs:	
phenylbutazone antihistamines analgesics antimigraine products	Reduced OC efficacy has been reported. Remains to be confirmed.

Table 5
Drugs Whose Action May Be Modified by Oral Contraceptives

Therapeutic Agent	Mode of Action
Aminocaproic acid (inhibitor of fibrinolysis)	Theoretically, a hypercoagulable state may occur because OCs augment clotting factors. Should not be given with OCs.
Anticoagulants	Because the estrogen component augments coagulation factors, increased dosages of anticoagulants may be required. Paradoxically, OCs potentiate the action of anticoagulants in some patients.
Anticonvulsants	Fluid retention may precipitate seizures in epileptics. OCs may also enhance the activity of anticonvulsants.
Antihypertensives:	
guanethidine	Antihypertensive effect is reduced.
methyldopa	Estrogens cause sodium retention.
beta blockers	Increased drug effect due to decreased metabolism.
Betamimetic drugs:	
isoproterenol	Estrogens cause decreased response to these drugs.
Corticosteroids	Estrogens enhance anti-inflammatory activity. This may retard the metabolism of cortisol. Excessive corticosteroid effects should be watched for.
Cholesterol lowering agents:	
clofibrate	The action of these agents may be antagonized by OCs.
Meperidine	Possible increased analgesia and CNS depression due to decreased metabolism of meperidine. Use combination with caution.
Oral Hypoglycemics, Insulin	OCs may decrease glucose tolerance and increase blood glucose. Increased dosage of hypoglycemic medication may be required.
Tranquilizers:	
phenothiazines reserpine	Estrogens potentiate the hyper-prolactinemic effect of these drugs which may cause mammary hypertrophy and galactorrhea. Also, potentiation of the ataractic effect of promazine has been reported, possibly due to enzyme induction.
chlordiazepoxide diazepam lorazepam oxazepam	Increased effects of these drugs may occur due to decreased metabolism.
Alcohol	Increased blood levels of ethanol or acetaldehyde have been reported.
Folic Acid and Vitamin B_{12}	OCs have been reported to impair folate metabolism and reduce serum levels of vitamin B_{12}

Table 6
Drugs That May Potentiate the Adverse Effects of Oral Contraceptives

Therapeutic Agent	Mode of Action
ASA Allopurinol Chloramphenicol Disulfiram Isoniazid Methylphenidate MAO inhibitors PAS Phenothiazines	These drugs all may cause hepatic enzyme inhibition which may potentiate the action of OCs by delaying their metabolism. This may increase the incidence or severity of adverse effects of OCs.

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COMPLICATIONS OF ORAL CONTRACEPTIVE THERAPY

The material contained in the following sections is not meant to be a comprehensive review of the adverse effects associated with the use of OCs. Rather, current knowledge is presented in areas of major concern such as cardiovascular system effects and possible relationships between OCs and the development of cancer. Other subjects of continuing interest are also discussed. It is hoped that this information will prove to be useful to physicians and their patients in the proper use of OCs.

1. ORAL CONTRACEPTIVES AND CARDIOVASCULAR SYSTEM EFFECTS

Venous thromboembolism, myocardial infarction and cerebrovascular disease and arterial thrombosis are 3 major areas upon which numerous studies have been published relative to OCs and their adverse effects.[1] Recent evidence, particularly relating to age and smoking, would indicate that there are important additional risk factors for vascular disease among women receiving OCs.[1,2,3]

Venous Thromboembolism

Superficial thrombophlebitis, deep venous thrombosis and pulmonary embolism are increased in women who are users of OCs. There is a 2 to 4 times increased risk in users but the opportunity for detection bias when clinical diagnosis is used alone suggests that even this increased risk may be an overestimate.[1,4]

There is no correlation between venous thromboembolism and total duration of use or previous use of OCs. The presence of varicose veins in the absence of previous deep venous thrombosis also is not a risk factor.[5] Smoking does appear to increase the risk of venous thromboembolism but this effect is less marked than the increased risk observed for arterial disease.[5]

The discontinuation of the use of OCs in a woman who is to have major elective surgery should be planned 4 to 6 weeks prior to admission to the hospital. If this is not feasible, minimum precautions should include the discontinuation of the use of OCs as soon as possible and the administration of prophylactic heparin subcutaneously during the hospital stay. In the absence of complications, OCs may be restarted 2 weeks after discharge from the hospital.

Myocardial Infarction

There is evidence that the use of OCs is associated with an increased risk of circulatory disease mortality and morbidity. Recent publications have clarified the specific risk factors that are operative. Age and smoking as modifiers of the relative risk have been the subject of several major studies and their conclusions may be summarized as follows:

1. The number of deaths from arterial disease among women who have ever used OCs is approximately 4 times greater than that in women who have never used OCs[1,2] (see Table 7).
2. Ischemic heart disease is more frequent in ever-users than in never-users of OCs.[1]
3. The risk of mortality from arterial disease has been correlated with age and smoking in women who are OC users (see Figure 4).
4. There is no correlation between the incidence of arterial disease and the duration of use of OCs[1] (see Table 8).
5. The finding from a recent report from the Royal College of General Practitioners Oral Contraceptive Study[1] that there is an increased risk in OC ever-users from circulatory disease mortality, as parity increases, and that this increased risk is independent of age, smoking or other variables is new and important information.

Physicians and patients should be aware of this new information which requires confirmation by the results of ongoing studies. These findings should be taken into consideration in patients of high parity, even if they are young or are non-smokers, who should be counselled and managed appropriately.

Cerebrovascular Disease

There is an increased risk of thrombotic and hemorrhagic stroke in women using OCs and this is further increased by smoking. For current users of OCs, the relative risk of stroke was found to be 3.2. For former users it was 4.5. In addition, 71% of the everusers and 67% of the controls who died of subarachnoid hemorrhage were smokers compared to 48% of all ever-users and 40% of all controls who were non-smokers.[5]

Women who present with unexplained central nervous system symptoms, which might indicate thrombotic or hemorrhagic events, should discontinue the use of OCs. These warning symptoms may include transient numbness at the side of the tongue, speech defects, loss of vision, periodic weakness of a limb, a change in the character of a migrainous attack, or major symptoms of a stroke. The use of OCs in patients with recognized risk factors for cerebrovascular disease, especially in older women or in those who are heavy smokers, is not recommended.

Hypertension

Many observers have pointed out that the use of OCs is associated with a modest but definite rise in blood pressure, especially systolic blood pressure, which is related to the patient's age and the duration of use.[7,8] Hypertension does not appear until after 3 to 9 months of OC use. All women who are given OCs should, therefore, have blood pressure recordings at regular intervals during the first year of medication and at every subsequent visit. They also should

Table 7
Deaths from Circulatory Disease (ICD 390-458) Among Ever-users of Oral Contraceptives and Controls, by Parity[1]

Parity	Mortality rate (no. of deaths)		Relative risk (95% confidence limits)	Excess risk (95% confidence limits)
	Ever-users	Controls		
0	0.0 (0)	10.0 (3)	0.0	−10.0 (−108.0.0,88.0)
1-2	22.7 (20)	5.5 (5)	4.2(1.5,11.6)	17.2 (5.1,29.5)
3	42.8 (35)	5.7 (2)	7.5(2.8,19.8)	37.1 (19.4,55.6)
TOTAL	29.9 (55)	7.2 (10)	4.2(2.3,7.7)	22.7 (13.2,32.2)

Standardised for age, smoking and social class.

Table 8
Circulatory Disease (ICD 390-458) Mortality Rates Per 100 000 Women-Years, by Total Duration of Oral Contraceptive Use[1]

		Total duration of oral contraceptive use (mo)				
	Controls	1-24	25-48	49-72	73-96	97 plus
Rate (no. of deaths)	7.0 (10)	32.5 (5)	23.5 (4)	28.4 (5)	32.3 (5)	20.4 (4)
Relative risk	1.0	4.6	3.4	4.1	4.6	2.9

Standardised for age, parity and smoking status.

be instructed to report any abrupt increase in weight which is an indication of sodium and water retention and sometimes accompanies an increase in blood pressure. If a significant elevation of blood pressure occurs (20 mm Hg systolic and/or 10 mm Hg diastolic), the OC should be withdrawn and an alternate method of contraception prescribed. In young, healthy patients, the blood pressure will usually return to normal within 3 months. Oral contraception may be cautiously resumed, but with very careful monitoring. If the blood pressure does not return to normal, or if it increases again on resumption of medication, this method of contraception might contribute to the early development of hypertensive vascular disease and therefore should not be used.

Notwithstanding the above, OCs may be prescribed for young, healthy women who have mild, stable hypertension, provided that frequent monitoring of blood pressure is performed. We do not recommend OCs for patients who have moderate or severe hypertension.

On the basis of current information, we recommend that a combination OC containing a low dosage of both estrogen and progestogen be prescribed, whenever clinically suitable, to minimize the incidence of vascular complications.

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2. ORAL CONTRACEPTIVES AND CARCINOGENESIS

Introduction

The possible relationship between OCs and carcinogenesis is difficult to evaluate for several reasons.

Cancers often have long, latent periods of 5-30 years between exposure to a carcinogen and detection of the disease.

Estrogens and progestogens have different effects upon different tissues. These effects may vary from one person to another and with the age of the patient.

Neoplasia of the breast and reproductive organs is influenced by many factors including sexual behaviour and reproductive history, thus compounding the difficulty of determining the possible neoplastic effects of OCs.

Breast cancer and cervical neoplasia are common. Many subgroups of patients of different ages, family histories and fertility patterns can be studied. Some relationships which appear must seem statistically significant, but are actually owing only to chance.

Cervix

A large number of epidemiological studies have addressed the question of a relationship between OC use and the development of cervical neoplasia (cervical dysplasia, carcinoma in situ and invasive carcinoma). Most studies have failed to reveal an etiologic association when known risk-factors were controlled.[1,2] One study[3] has suggested that progression of an established dysplasia may be accelerated by OCs but this finding remains to be confirmed. A recent publication from the Oxford Family Planning Association[4] has reported a greater risk of cervical neoplasia in women using OCs than in women using intra-uterine devices. An increase of dysplasia in OC users also was found in a Canadian study[5] which corrected for age at first coitus. Unfortunately, in these and many other studies, information concerning major risk factors is incomplete and therefore the conclusions are in doubt.

The major risk factors for cervical neoplasia are multiple partners[6,7,8] and young age at first intercourse. There is evidence that cigarette smoking also increases the risk of cervical dysplasia and carcinoma.[7,8] Human papilloma virus infection is another risk factor for cervical neoplasia[9] with certain strains being oncogenic for the female genital tract.[10] Meisels[11] has speculated that there may be an interaction between human papilloma virus infection and the use of oral contraceptives in cervical infection and the use of oral contraceptives in cervical carcinogenesis but this remains to be established. Unfortunately, most publications that discuss cervical neoplasia and use of OC fail to mention that a diagnostic distinction has been made between changes due to dysplasia and due to human papilloma virus. The risk attributed to use of OC and duration of use appears to be explained by the above major risk-factors.

In summary, it does not seem likely that women who use OCs are at increased risk for cervical neoplasia. It is clear, however, that women who have had sexual intercourse are at risk. Annual screening of patients aged 18 to 35 has been recommended by the task force on cervical cancer screening programs in Canada.[12]

Endometrium

The use of combination OCs has been reported to decrease a woman's risk of developing carcinoma of the endometrium.[13] The protective effect is seen after 12 months and, in some studies, has persisted for some years after cessation of use. Sequential OCs, no longer available in Canada, were infrequently associated with the development of endometrial adenocarcinoma in young women.[14] These latter cases serve to emphasize the importance of appropriate dosage and dosage ratio of the component hormones and also the importance of careful patient selection.[15]

Ovary

No statistically significant differences in the incidence of use or duration of use of OCs between women with ovarian cancer and controls were found in 1 analysis of possible risk-factors for ovarian carcinoma.[16] Other studies[17,18] have demonstrated a reduced risk of cancer of the ovary in women who have used OCs, which could not be accounted for by parity, infertility or other known risk factors.[18]

One case-control study has found a decreased risk for ovarian cancer associated with past use of OCs in women who were 40-59 years old; the risk for women under 40 was the same in users and never-users.[19]

Liver

Hepatic tumors have been reported in women who use OCs.[20,21] Two main types of lesions have been described: focal nodular hyperplasia (also referred to as hepatic hamartoma) and liver cell adenoma. There is now good epidemiologic evidence of an increased incidence of liver cell adenoma in OC users. The tumors are associated with long-term use of OCs[22] and there is a striking increase in relative risk after 7 years of use.[23] Liver cell adenomas remain rare, but they should be considered in OC users who have abdominal signs or symptoms because these lesions may rupture and cause intra-abdominal hemorrhage. The incidence of focal nodular hyperplasia is probably

Table 9
Estimates of Relative Risk of Cervical Dysplasia for Oral Contraceptive Use Adjusted Separately for Lifestyle Factors Using Matched Logistic Regression Techniques (239 cases and 441 controls)[8]

Model	Estimates of relative risk				
	OC Use	OC use† Years of education	OC use† smoking status	OC use† age at first intercourse	OC use† no. of sexual partners
OC use, ever vs never	2.6*	2.5*	2.7*	2.3*	1.7†
Years of education, ≤13 vs >13		1.6‡			
Smoking status					
current vs never			3.1*		
ex-smoker vs never			1.1		
Age at first intercourse, <18 vs ≥18 yr				2.8*	
No. of sexual partners					
2-5 vs 1					3.4*
≥6 vs 1					6.9*

* $P < 0.01$
† $P \leq 0.14$
‡ $P < 0.05$

not increased in OC users although it appears that lesions, in women who use these compounds, are more likely to have hemorrhagic complications[21,24] that might be accentuated in women who smoke.[25] Hepatocellular carcinoma may occur in OC users[26] but this is a rare occurrence. There is no evidence to indicate that it is more common than in women who do not use OCs.

Breast

Carcinoma of the breast is so frequent that even a small increase in relative risk would result in a large number of additional cases. Numerous studies have addressed the question of whether or not the use of OCs alters the incidence of breast cancer. In general, the findings have been reassuring. Several studies involving large numbers of women have not shown an increased risk of breast cancer in OC users.[27,28,44] Concern remains, however, especially in certain subgroups of women known to have major risk-factors for breast cancer such as older age at first pregnancy, a history of benign breast disease and a family history of breast cancer.[29,30]

(a) Age at First Full-term Pregnancy

The risk of breast cancer increases with advancing age at which a woman bears her first full-term child.[29,31] Women first parous before the age of 18 have about one-third the breast cancer risk of those whose first delivery is delayed until the age of 35 or older.[29] The incidence of breast cancer also falls with increasing parity.[31] Lactation has little or no effect on breast cancer risk.[29] Delay of the first birth, a major risk factor for breast cancer, is often the result of OC use. If this factor is not taken into account, a spurious association between the pill and breast cancer may be suggested.

However, 3 groups of investigators have found an increased relative risk of breast cancer at a young age in case-control studies of women who used OCs before first childbirth[32,33] or before the age of 25.[34] A recent analysis by the Oxford Group of an ongoing case-control study also has shown an increased risk of breast cancer in women who used OCs before first full-term pregnancy.[35] The magnitude of risk increased with increasing duration of use. They could not confirm a specific association with the type of OC nor with use before the age of 25. In contrast, no significant increase in breast cancer before first full-term pregnancy in OC users was found in an on-going study in the USA[28] when age at first full-term pregnancy and menopausal status were controlled.

If breast cancer is induced by OCs, there may well be a long, latent period before development of the disease. The year in which OCs were first used by large numbers of women has varied from country to country and from one community to another. We must, therefore, understand that studies of different population groups may lead to differing conclusions. Furthermore, well-controlled studies are required before conclusions can be drawn concerning breast cancer risks for OC users compared to women using other methods for delaying a first pregnancy.

(b) Progestogen Potency

The increased risk of breast cancer before first full-term pregnancy has been linked to the use of OCs judged to have "high progestogen potency"[34] but this has been seriously questioned. In addition to progestational effects, progestogens may have estrogenic, anti-estrogenic and even androgenic activities. Assessment of potency of these individual properties is not possible.[36] The problem is compounded by the additional biologic effects of the

estrogen component in OCs. Current methods for assessing progestogen potency measure the effect of the hormone on human endometrium, specifically the delay induced in menses.[37,38] It is difficult to evaluate the relevance of this test to carcinogenesis in the breast.

(c) History of Benign Breast Disease

A history of benign breast disease is another recognized risk-factor for breast cancer. There is a spectrum of histologic changes that may be seen in breast biopsies that are classified as benign; changes range from simple cysts to atypical epithelial hyperplasia. There is growing awareness that only the latter is associated with subsequent breast cancer.[39] In women who use OCs, the overall incidence of symptomatic fibrocystic disease is lowered. A histologic study of biopsy specimens[40] has shown that this decrease in incidence relates only to fibrocystic disease in which epithelial atypia is minimal or absent. The frequency of fibrocystic disease with marked atypia is the same in long-term users and never-users of OCs. In other words, the use of OCs protects against the forms of fibrocystic disease that are not firmly associated with an increased risk of breast cancer, but not against the pre-malignant forms. The incidence and histologic appearance of fibroadenomas of the breast are similar in women who use the pill and in women who do not.[41]

Two case-control studies have failed to show an increased risk of breast cancer in OC users with a history of biopsy-proven benign breast disease.[28,42] However, an increased relative risk of breast cancer has been reported in women who have had 2 or more biopsies after starting to use oral contraceptive hormones.[42]

(d) Family History of Breast Cancer

An increased risk of breast cancer is found in women with a family history of this disease on either the maternal or paternal side. Cases with a positive family history also occur with increased frequency among younger women. In 1 study,[43] it was found that current OC use increased the risk of invasive breast cancer among grandmother- or aunt-positive women; this association was less marked when the mother had breast cancer and was not evident when the positive family history was sister only. On the other hand, OCs significantly decreased the risk of breast cancer among women with no family history of the disease. If confirmed by other studies, this type of analysis might define subsets of women in whom the risk of breast cancer may be increased or decreased by OC use. At the present time, however, the findings of epidemiologic studies concerning OCs, family history and breast cancer are variable. Some emphasize the significance of a sister-positive history[42] while others find no association with any particular family member.[28]

(e) Established Breast Cancer

In addition to a possible effect on the development of breast carcinoma, the effect of OCs on established breast cancer warrants consideration. These neoplasms are often hormone-dependent. OCs are contra-indicated in women with breast cancer, but it is a matter of concern that women with pre-clinical breast carcinoma might inadvertently use estrogen-progestogen preparations.

(f) Summary

The frequency of breast cancer increases to a peak at 45-49 years and then decreases to a level which is constant in older age-groups.[43]

Conclusions drawn from current literature about OCs and breast cancer must be viewed with this in mind and be tempered by an awareness of the long latency of human cancer.

Although oral contraception lowers the incidence of certain benign lesions and might even protect against the development of carcinoma in certain subsets of women, those who develop palpable lesions while taking OCs must be regarded as at risk for breast cancer.

All women should be instructed in self-examination of the breast when OCs are first prescribed. At this time, a thorough examination of the breast by the physician will establish a baseline for future examination.

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3. ORAL CONTRACEPTIVES, PREGNANCY, AND FETAL ANOMALIES

The possibility of birth defects resulting from exposure of the fetus to female sex hormones has been one of the most controversial issues over the last 20 years. In an attempt to bring some order to this subject, the World Health Organization convened an expert Scientific Committee to examine the effect of female sex hormones on fetal development and infant health. The committee met in 1979 and their recommendations were published in 1981.[1]

Female sex hormones have been used in the treatment of a number of conditions, such as habitual or threatened abortion, premature labor, infertility and dysmenorrhea. However, they are most widely used as contraceptives, either in the form of tablets or long-acting injectables.

OCs exert their effect by interfering with the normal reproductive cycle. There is a suppression of follicular maturation and of cyclical development of the endometrium, the latter becoming thinner and less glandular.

In considering the risk of fetal anomalies in association with the use of OCs, it is necessary to distinguish between a pregnancy that occurs immediately after discontinuing the use of the contraceptive and use of the pill during a conception cycle and after conception, as a result of method failure.

Pregnancy Immediately After Discontinuing Oral Contraceptive Use

There is no evidence that the fertility of former OC users is impaired. There may be a delay of up to 3 months in the reestablishment of normal ovulatory cycles.

A pregnancy which occurs immediately after discontinuing the use of OCs raises the possibility of a "carry over" effect that may interfere with physiological function and so influence oocyte maturation or the quality of the endometrium.

Assays of plasma protein and steroid hormones suggest that while the majority of women ovulate during the first cycle after stopping the pill, the LH peak or surge which results in the rupture of the follicle and release of the oocyte in this cycle is slightly delayed. The first cycle, therefore, may be longer than usual, even up to 6 weeks. The gestational dates of ongoing pregnancies may be inaccurate according to the usual calculations and it may appear that women who discontinue the use of OCs and then become pregnant have an excess of post-term deliveries. However, there is no other evidence of post maturity such as increased birth weight in these babies.

One large prospective study from the U.S. National Institute of Child Health and Human Development[2] has shown no increase in total malformations in infants conceived immediately after the use of OCs was discontinued. Two recent studies[3,4] have suggested that there may be an increased risk of spontaneous abortion of a pregnancy conceived within 1 month of stopping OCs, but this risk is not significant. Evidence that these abortions are the result of chromosomal abnormality in the embryo is inconclusive. The studies by Carr demonstrated an excess of lethal triploid conceptuses,[5] but Boue[6] and Lauritsen[7] showed no excess of chromosomal anomalies after recent pill use.

In summary, women who discontinue the use of OCs immediately prior to conception appear to have no increased risks of a child with a birth defect or perinatal death, prematurity, low birth weight, change in the male/female sex ratio, or perinatal morbidity.

Oral Contraceptives Used During and After the Cycle of Conception

The probability that a woman will become pregnant while taking OCs is thought to be 1 per 1000 women-years

of use. However, the observed frequency of pregnancy in women taking OCs is about 1 per 100 women-years. This results in approximately 20 000 pregnancies per year in Canada.

Most of the reports of birth defects in association with the use of the pill are anecdotal or the result of poorly-controlled studies containing small numbers of patients and relying too heavily on memory of previous events.

The birth defects that have been reported in association with exposure of the fetus to OCs are chromosomal anomalies, heart and limb anomalies, and a variety of other malformations.

1. Chromosomal Anomalies

These are a serious risk, but one which could be monitored by prenatal diagnosis if valid. A Californian case-control study of 814 births following OC breakthrough conception reported a small but non-significant increase in trisomy 18 in the exposed group.[8] This is virtually the only study in which the methodology was sufficiently satisfactory. The question of whether or not there is a significant risk of chromosomal anomalies will remain until further data become available.

2. Heart and Limb Anomalies

There are several reports of case-control and cohort studies of congenital malformations in which the methodology is reliable. The studies include those of Janerich,[9] who looked at limb reduction anomalies, and Rothman[11] and Heinonen,[12] who looked at heart anomalies. Janerich found a small but non-significant increase in limb anomalies. Similarly, Rothman and Heinonen found a small but non-significant increase in heart anomalies. The risk of a heart anomaly is approximately less than twice that in the general population or about 1 per 1000 exposed newborns. The Royal College of General Practitioners in England has carried out the largest prospective study and found a decreased risk of malformations in exposed fetuses.[13] The evidence suggests that there is no current consensus concerning the risks.

The Scientific Committee of the World Health Organization addressed these issues and its conclusions were: (a) that there may be a slight increase in the risk of spontaneous abortion, (b) the evidence for increased risk of congenital malformations is not clear, (c) if such risks exist, they are very small and are possibly related to malformations of the heart and limbs.

General Recommendations to a Patient

1. Discontinue the use of OCs and delay pregnancy until at least 1 normal spontaneous cycle has occurred.
2. If a pregnancy occurs while taking OCs and if the fetus is exposed during the first 3 months of pregnancy, the empirical risk of a defect may be raised slightly from 2-3% to 4%, with particular emphasis on heart and limb anomalies.

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4. ORAL CONTRACEPTIVES AND THE ENDOCRINE SYSTEM

Galactorrhea

Because there is some evidence to suggest that estrogens, both endogenous and exogenous, may stimulate the growth of the pituitary adenomas which produce prolactin, it is suggested that undiagnosed galactorrhea should be considered to be a relative contra-indication to the use of OCs.[1,2]

On the other hand, concern that exogenous estrogens, particularly in the form of OCs, might play a causal role in the induction of such tumors, has not been substantiated.

Although further evidence may be accumulating to clarify this matter, it is reasonable to state at this time, that the evidence strongly supports the fact that there is no etiological relationship between OC use and pituitary prolactinomas.[3,4] However, amenorrhea, which is a common presenting symptom of such disease, will be masked by the withdrawal bleeding induced by an OC. The committee does suggest that the appearance of galactorrhea while on OCs merits investigation.

Amenorrhea During Oral Contraceptive Use

By physiological standards, the combination OC usually produces an excessive progestogen effect upon the endometrium. Ordinarily, this results simply in a reduction of menstrual bleeding. However, in a small percentage of patients, the endometrial suppression is of such a degree that no withdrawal bleeding may occur. In this situation, the possibility of pregnancy must be excluded as soon as possible. This can be aided considerably by the use of a beta HCG pregnancy test done on a first morning urine sample.

It is obviously of importance to resume contraception quickly if there is no evidence of pregnancy.

This harmless form of amenorrhea has no relationship to postpill amenorrhea or future infertility. Having excluded pregnancy initially, there is no evidence of an increased risk of becoming pregnant under these circumstances, assuming the patient continues to take the same medications as directed.

However, in a situation where a woman is disturbed emotionally by the continued amenorrhea, it may be necessary to switch to a more estrogen-dominant type of OC.[8]

Post-Pill Amenorrhea

The incidence of amenorrhea that lasts more than 3 months after discontinuing the use of OCs has been reported to be 1% or less. Indeed, this seems to be very similar to the incidence of spontaneous amenorrhea in nonusers of OCs.[9]

Patients who have a history of menstrual abnormalities, or extreme variations in bodyweight, are much more prone to develop post-pill amenorrhea. Most reports in the literature are in agreement that spontaneous amenorrhea and post-pill amenorrhea are the same condition and that full investigation is necessary, if amenorrhea has lasted more than 6 months.[10] The probability of amenorrhea developing after cessation of therapy with OCs does not appear to be related to the duration of use of these products. It is recommended, therefore, that a history of menstrual disturbance is not a contra-indication to oral contraception, except in very young women who have oligomenorrhea associated with infrequent ovulation. In fact, in certain patients, e.g. those who have polycystic ovaries, OCs may be the desired form of therapy to prevent progression of hirsutism, alleviate excessive bleeding episodes, and prevent early development of endometrial carcinoma. It is unfortunate that so many women develop feelings of extreme guilt concerning their fertility when amenorrhea arises. One should make every attempt to dispel these feelings by assuring them that, with therapy, their prognosis is no different than if they had never taken OCs.

Amenorrhea and galactorrhea may present after discontinuing the use of OCs. This demands a thorough investigation to identify the cause before initiating treatment.

Thyroid Function

Although OCs may cause alteration in certain thyroid function tests, these are not felt to induce significant alterations in the clinical thyroidal state of users. It is, however, very important for the clinician to know the effects of OCs upon test results when investigating patients who are under treatment (see Table 10).

The reason that OCs are not involved in the induction of hyperthyroidism or hypothyroidism is likely the fact that the estrogen causes an increase in the protein fraction, but does not increase the free (hormonally active) thyroxine level. This also results in the inverse effect seen in the T_3 resin uptake test. These changes are similar to those seen in early pregnancy and when the medication is withdrawn, may require 6-10 weeks to revert to their original levels. Serum TSH and T_3 radioimmunoassays are unchanged or show a slight increase.[6].

Table 10
Effect of Oral Contraceptives on Thyroid Function Tests[5]

	Untreated (n = 19)	OC users (n = 17)
Total T_4 (mcg/dL)	8.7 ± 0.5	11.9 ± 3.3
Free T_4 index	2.5 ± 0.2	3.0 ± 0.7
Free T_4 (ng/dL)	1.2 ± 0.2	1.2 ± 0.3
T_3 resin uptake (%)	28.9 ± 1.6	25.3 ± 1.7

Adrenal Function

Since OCs were first used in their original high dosage form, the impact on adrenal function has been of some interest. However, perhaps the "bottom line" is the fact that no clinical reports of significant adrenocortical insufficiency, due to OC use, have been published in recent years.

Amin et al[7] showed that 50 mcg of ethinyl estradiol plus 1 mg norethindrone caused an increase in serum cortisol at 3 months, with no further change at 6 and 9 months. On the other hand, urinary cortisol levels remained unchanged, while 17-ketosteroids and 17-ketogenic steroids diminished

at 3 months with no further change up to 9 months. No change in any of the above parameters was noted with an OC containing the same amount and type of progestogen, but only 20 mcg of ethinyl estradiol. These data suggest that the observed alterations were likely related to the estrogen content.

In all likelihood, the major impact of the combination OC is due to an increase in the protein-bound cortisol fraction which is nct hormonally active. On the other hand, the diminished urinary 17-ketosteroids is due in part to a significant decrease in ovarian androgens.

It is felt that the OCs currently marketed have not posed any significant risk due to altered adrenal function.

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5. ORAL CONTRACEPTIVES AND INFECTIONS

The increased incidence of sexually transmitted diseases in the last 2 decades has been ascribed to the increasing use of OCs. However, a definite cause and effect relationship has not been established. This section will examine the relationship between OCs and the more commonly encountered infections.

Gonococcal Infections

Gonococcal infections may be confined to the cervix, urethra, or other mucosal surfaces such as the rectum or oropharynx. The organisms may remain undetected for long periods of time in asymptomatic patients.

Cervical infections may spread, particularly at or after menstruation, resulting in salpingitis, peritonitis, and/or abscess formation. The majority of peritoneal disseminations are gonococcal in origin but other organisms may be involved. Rupture of an abscess with ensuing peritonitis can be life-threatening, but a recent review[1] of 23 000 OC users failed to reveal any mortality from infections that might have been associated with the use of these products.

Published reports have shown a reduced incidence of acute pelvic inflammatory disease among OC users compared to that in non-users.[2,3] In one study, the relative risk of PID ranged from 0.3 to 0.9.[1] It was 0.5 in a large multicentre case-control study where OCs had been used in the 3 months prior to entering the study.[3]

The influence of OCs upon localized disease of the cervix has not been clarified.[4] It has been suggested that the reduced incidence of salpingitis may be related to a protective effect of OCs whereby there is a compaction of glycoproteins in the cervical mucus, and/or a reduced menstrual flow, thus creating unfavorable conditions for the upward spread of infection.[6,7] A reduced admission rate to hospital for patients with a diagnosis of PID has been reported among OC users compared to non-users (Figure 3).

Candidal Infections

OC users carry an increased risk of acquiring candidal infections of the vagina. The infection may be difficult to eradicate while oral contraception is being continued. Occasionally, OCs may have to be stopped and an alternate method of contraception selected in order that the infection may be treated effectively.[4] OCs usually may be reinstituted after treatment but occasionally their use may have to be discontinued permanently.

Trichomonal Infections

Trichomonal vaginitis is a common vaginal infection. OCs seem to have little effect upon its incidence. What evidence there is suggests that OCs may reduce the risk slightly.

Gardnerella Infections

The infectivity of Gardnerella vaginalis does not appear to be influenced by OCs.

Chlamydial Infections

Chlamydia trachomatis as a cause of cervicitis, salpingitis, non-gonococcal urethritis, neonatal eye infections, and neonatal pneumonia has been studied increasingly in recent years. There is evidence to suggest that the incidence of chlamydial cervicitis may be enhanced by OCs.[5]

"Pill Cervix"

With the use of combination OCs, the cervix hypertrophies and the endocervical canal undergoes eversion, thereby exposing the endocervical columnar epithelium. The cervical mucus becomes more tenacious and turbid. The rather florid appearance of the cervix requires no therapy and the cervix reverts to normal once OCs have been withdrawn.

Urinary Tract Infections

Takahashi and Loveland, in 1974, studied the prevalence of asymptomatic bacteriuria in 12 076 non-pregnant women.[8] The results showed an incidence of 1.6% in non-users of OCs, 1.8% in those who had used the pill in the past, and 2.4% in those currently using OCs. They concluded that there was a statistically significant increase in the number of patients with asymptomatic bacteriuria who were taking OCs. They also showed that the commonest infecting organism was E. coli.

On the other hand, there is conflicting evidence on the incidence of clinical urinary tract infections. The Royal College of General Practitioners' study[9] found significantly higher rates, while the Walnut Creek study[10] did not.

It is recommended that urinalyses be performed when patients are being placed on OCs and annually thereafter. If bacteriuria is found, a mid-stream urine sample should be taken for culture and the patient treated appropriately.

Tropical Diseases

Since immigrants to Canada may come from many tropical countries, the interaction of OCs with tropical diseases should be considered. Among the many tropical diseases, schistosomiasis (bilharziasis) and in Asia, liver fluke (opisthorchis viverrini) are very common. The results of liver function tests remain the same in OC users, whether they have tropical diseases or not. Patients with tropical disease, in general, should not discontinue using their contraceptive pill, even while under treatment, but should be checked frequently.

Caries and Gingivitis

Cebi[11] found no relation between dental caries and OC use, but gingivitis has been shown to increase with the use of OCs.[12] Further work will be required before any long-term effects become established.

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6. ORAL CONTRACEPTIVES AND OCULAR EFFECTS

Numerous reports have appeared in the medical literature of ocular adverse effects associated with the use of OCs.[1,2] The problems most commonly seen include intolerance to the use of contact lenses manifested by subjective discomfort and change in visual acuity, increased incidence of ophthalmic migraine, and occasional retinal vascular occlusive incidents.

Patients who complain of contact lens intolerance should be instructed to discontinue using these lenses and undergo full ophthalmological assessment. Migraine patients using OCs who develop increasing frequency and severity of associated eye symptoms should be examined ophthalmologically for evidence of retinal, vascular and/or neurological changes. Sudden changes in visual acuity or field of vision in OC users should be assessed for evidence of occlusion of the central retinal artery or vein, or branches thereof, and appropriate referral and treatment instituted.

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7. ORAL CONTRACEPTIVES AND MIGRAINE

In childhood, the male to female ratio for migraine is 1:1 whereas, in adults, female cases are 3 times as common. Migrainous symptoms fluctuate with the menstrual cycle and are worse at the time of menstruation. In contrast, migrainous symptoms often improve during pregnancy. Headaches are a frequent complaint of OC users and may be of sufficient severity to cause cessation of taking the pill.[1] Studies on known migraine sufferers have shown an increase in both the frequency and severity of the migrainous attacks when the contraceptive pill is taken.[2] The mechanism by which OCs can exacerbate migrainous symptoms is not known; however, the increase in frequency of severity of symptoms will cease when the medication is discontinued. Patients who have had migrainous symptoms in the past may be prescribed OCs since not all patients will experience an exacerbation of symptoms. If the pill is prescribed to a migraine sufferer, careful note should be made of any increase in the severity of symptoms. If this occurs, the medication should be stopped. There are isolated case reports associating the use of OCs with both exacerbation of migrainous symptoms and development of retinal and cerebral insufficiency.

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8. ORAL CONTRACEPTIVES AND DEPRESSION

Because of non-objective data and a multiplicity of variables, evaluation of psychiatric disturbances attributed to OCs is difficult.

In an excellent review, Slap[2] summarized 12 major studies carried out between 1967 and 1978 and her conclusions were as follows. The major problem of the clinical trials was selection bias, poor assessment of premorbid mood states, and an unclear definition or measurement of depression. Nine of these major studies of the association between OC use and depression reported depression in 16-56% of women using OCs. Three studies, incidentally among the most recent, found no association between OC use and depression. The 2 reports with the higher prevalence of depression were case studies, employing neither placebo trials nor control groups.

The randomized double-blind experiment of Cullberg[3] and the prospective cohort study of the Royal College of General Practitioners[4] suggest a 10-15% increase in depression among women using OCs as compared with women not using these compounds.

Chang et al[1] point out that oral contraceptive depression is not characterized by other recognized symptoms of depression such as guilt, low self-esteem, hopelessness and sadness. The emotional disturbances, cited as depression, may be rather better characterized as dissatisfaction. This

dissatisfaction is expressed as anger and frustration at the physical side effects, such as bleeding, weight gain and headache, and emotional effects such as the annoyance of having to take a pill every day, or anxieties about the possible danger of the pill.

There is as yet no clear concensus as to which component of the oral contraceptive pill is associated with depression.

Progesterone in large dosage produces a sedative effect. Southgate et al[5] showed that endometrial monoamine oxidase (MAO) activity increased tenfold during the late secretory phase of the menstrual cycle. The effectiveness of MAO inhibitors as antidepressants immediately incriminates MAO and therefore depression was thought to be associated with excess progestogen.

Other authors suggest that the progestogen content is of minor significance in causing depression.

Estrogen, on the other hand, can affect the formation of serotonin and catecholamines in the central nervous system by several mechanisms and may therefore play a role in the development of depressive symptoms.[6]

It is thought that estrogen may produce a functional vitamin B_6 deficiency which leads to reduced amounts of pyridoxal-5-phosphate, an essential enzyme in the biosynthetic pathway from tryptophan to serotonin.[7] This interference in the production of serotonin predisposes to depression.

Regardless of whether one is on the estrogen team or on the progestogen team, there is much less emphasis on the complaint of depression these days. There is some evidence that this is due to the gradual reduction in the amount of steroids in newer OCs currently on the market. In the Royal College of General Practitioners' Oral Contraception Study, the relative risk of neurotic depression in women taking OCs containing 30 or 35 mcg of estrogen, as opposed to that in non-users, was 1.00. Corresponding figures for products containing 50 mcg, 75 or 80 mcg, and 100 or 150 mcg of estrogen were 1.31, 1.74, and 1.80, respectively.[8] In this study, the possible influence of the accompanying progestogens contained in the various OCs could not be properly evaluated or eliminated.

Because depression, or mood change or dissatisfaction, are common conditions, they also may be expected to occur independent of OC use in some women who may be predisposed to depression, fatigue and premenstrual irritability.

Most patients who develop a frank psychosis or attempt suicide have a well-documented history of past psychiatric disturbances. They probably should not have been using OCs in the first place. It should be emphasized that women who appear emotionally disturbed, who have had previous episodes of depression or psychiatric treatment for these, or who are anxious about potential side effects of oral contraception, should be advised against its use. Usually, if the patient is questioned in this area, the physician will be forewarned and should consider the patient unsuitable for oral contraception.

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9. ORAL CONTRACEPTIVES, SOME CHANGES IN METABOLISM, AND ALTERATIONS IN CLINICAL LABORATORY TESTS

Carbohydrate Metabolism

Glucose is a source of energy in normal healthy individuals. Changes in glucose and insulin levels have been implicated in the development of atherosclerosis and diabetes, and are associated with an increased incidence of coronary heart disease and vascular disorders in women of child-bearing age. Variations in carbohydrate metabolism, together with changes in serum insulin and growth hormone, have been reported in several studies of women using OCs. The significance of these changes is difficult to interpret because of differences in drug composition, dosage and population groups.

Ovarian steroid hormones have been known to modify carbohydrate metabolism. In animal studies, estrogens have an effect upon carbohydrate metabolism, but to a degree that apparently is dependent upon the type of estrogen, the dosage schedule, and the carbohydrate status of the animal under treatment. According to human data, estrogens do not have a consistent effect upon glucose

tolerance and insulin secretion. The fasting plasma glucose may fall, gluconeogenesis may be impaired, liver glycogen may be increased and glycogenolysis reduced. Progesterone and progestogens increase the secretion of insulin and enhance pancreatic response.

As suggested by animal work, the inconsistencies observed in human studies may be explained by variations in the chemical nature of the OC, the dosage of the ingredients, the individual sensitivity to the metabolic action of the steroids, and the carbohydrate status of the individual. In 1963, Waine and colleagues[1] reported that OCs decreased oral glucose tolerance. Various authors have observed as much as a 25% increase in fasting blood sugar and a decreased glucose tolerance in 18 to 77% of treated subjects. Alterations in glucose tolerance were more pronounced in the oral test than in the intravenous test.

Investigators have measured insulin levels in conjunction with glucose tolerance in subjects taking OCs. The consensus appears to be that insulin levels are indeed elevated in such patients. In patients receiving OCs, fasting plasma insulin is higher and the increase observed after oral glucose is greater and more sustained even after an oral sulfonylurea test.[2] Thus, there seems to be a change in carbohydrate metabolism whereby an initial elevation in both blood glucose and insulin level is followed by a depression of the blood glucose and a persistent or further increase in the plasma insulin. The apparent increase in the plasma insulin could be explained by a relative insulin resistance. All of the following mechanisms have been described to explain the insulin resistance: 1. a decreased affinity of insulin receptors; 2. a reduction in the number of receptors; 3. significant changes in intracellular insulin metabolism; and 4. diversion from the liver of gluconeogenic precursors.

The combination OCs are especially responsible for an increased insulin resistance, an impairment of glucose tolerance, an increase in plasma insulin and growth hormone, and an elevation in non-esterified fatty acids (NEFA).[3]

Plasma growth hormone is increased by combination OCs.[4] In all cases, growth hormone levels decrease normally with increasing levels of blood glucose. Combination OCs appear to act on the hypothalamus, causing an increase in human growth hormone releasing factor which, in turn, stimulates the secretion of growth hormone from the anterior pituitary gland. Human growth hormone has an initial antagonizing action on glucose utilization which leads to an elevation of peripheral glucose levels. In turn, the increased glucose stimulates the pancreas to release more insulin. This pattern has been observed in the first 2 or 3 cycles of OC administration. The pancreas of the normal individual can compensate for increased growth hormone, and the resultant elevation of circulating insulin causes the blood sugar to return to normal or perhaps subnormal levels. This compensatory mechanism is observed about 3 months after one begins to use OCs.[5] Over long periods, certain individuals may develop decompensation of the islet cells. Among all progestogens, norgestrel appears to have the greatest insulin antagonizing activity.[6]

It is important to note that following the discontinuation of use of OCs there is usually a rapid and spontaneous resolution of abnormal glucose tolerance.[5]

Pre-diabetic and Diabetic Patients and Oral Contraceptives

Few studies have been conducted on diabetic, gestational diabetic, or non-insulin dependent diabetic patients. Spellacy[7] observed an improvement of the oral glucose tolerance after[6] months of norethindrone and 35 mcg of ethinyl estradiol. Skouby[8] found no deterioration of glucose tolerance in non-insulin dependent diabetics taking norgestrel. However, there was a significant increase in insulin levels in these patients. Radberg[9] found that OCs may interfere with dietary treatment of diabetes by increasing hunger and craving for carbohydrates. Therefore, it may be appropriate to consider an alternate method of contraception in diabetic or even pre-diabetic patients.

Lipid Metabolism

Water insoluble lipids are carried in the plasma in the form of lipoproteins. These lipoproteins are a mixture of triglycerides, cholesterol, phospholipids and a protein component. On the basis of centrifugation, lipids can be classified into 3 major components: very low density lipoproteins (VLDL), low density lipoproteins (LDL), and high density lipoproteins (HDL). High density lipoproteins are subdivided into HDL_2 and HDL_3.[10] The majority of cholesterol is associated with LDL and shows a positive association with athero-sclerosis. High density lipoproteins, in particular HDL_2, when decreased, are associated with premature atherosclerosis and when elevated appear to be protective against the development of athero-sclerosis.

The estrogenic and progestogenic components of OCs have very different effects upon triglyceride and cholesterol levels and also upon the levels and proportions of the various lipoprotein fractions.[10,11] Estrogens alone tend to cause a moderate rise in triglycerides, a mild rise in cholesterol (particularly the cholesterol associated with high density lipoproteins), and a concomitant decrease in low density lipoprotein cholesterol. These effects would appear to be potentially protective against the development of atherosclerosis. Progestogens, on the other hand, tend to cause very little change or even a decrease in the triglyceride levels, a decrease in high density lipoprotein cholesterol, and an increase in low density lipoprotein cholesterol. On balance these latter effects should be proatherogenic. The lipid effects of progestogens are dependent upon both the dosage and the type of progestogen and also the dosage of the associated estrogen.

The net effect of any oral contraceptive pill on serum lipids will be related to the relative amounts of estrogen to progestogen and to the types of estrogen and progestogen used. However, it has not been shown clinically that any one particular OC is associated with a higher incidence of atherosclerosis or premature cardiovascular disease.

The development of atherosclerosis is multifactorial and is dependent upon a complex interaction of heredity, lifestyle, and concomitant disease and its treatment. Changes in lifestyle factors such as smoking, alcohol consumption, bodyweight, and pattern of exercise can cause alterations in lipid levels that are outside acceptable, normal ranges.[12,13]

There have been numerous reports of changes in lipids associated with the use of OCs. e.g.[10, 11,14-17]. Some authors have suggested that combination OCs containing one or other progestogen may be atherogenic. Others have engaged in comparisons of progestogen potency which this committee does not consider scientifically valid because the effects of one progestogen cannot be directly compared with those of another. However, in the majority of these reports, particularly those which studied the low dosage combination OCs, the levels of serum lipids were not outside the accepted normal limits.[18] The clinical relevance of those alterations in serum lipids that were statistically significant has not been demonstrated.

Although distinctions cannot be made among the various combination OCs concerning a possible increased or decreased risk of atherosclerosis, it is always prudent to use the lowest dosage of any given progestogen in a combination OC that is consistent with effectiveness and good cycle control. It is also wise to carefully observe patients with a family history of hyperlipidemia or who have other predisposing factors for the development of abnormal serum lipid levels. Women who have excessively high levels of triglycerides or LDL cholesterol, or who develop these for whatever reason while taking OCs, should be considered for alternate methods of contraception.

Folic Acid Metabolism

Folate deficiency in women taking OCs is rare but both sequential and combination OCs have been incriminated in its occurrence.

Several researchers have reported contrary findings. Spray,[19] McLean,[20] Castren[21] and Pritchard[22] all failed to observe either a significant fall in serum folic acid, or an effect on folate metabolism in patients taking OCs. The type of contraceptive and the length of use, short or long, did not appear to have a significant effect. On the other hand, Sojania[23-25] observed a decrease in both serum and red cell folate, and also a higher 'Figlu' excretion. These alterations promptly disappeared after discontinuation of the contraceptive medication. Streiff[26] has described a folate deficiency anemia in some OC users, this being explained by a 50% decrease in the adsorption of polyglutamic folate. Finally, Holmes[27] reported that OCs are an unlikely cause of the megaloblastic anemia he observed in some patients; rather they should be regarded as a contributing factor in women who have occult malabsorption.

Liver Function

Jaundice has been reported in women using OCs. Impairment in the function of the bile secretory-excretory apparatus, sufficient to cause jaundice, is estimated to occur in 1:10 000 or fewer women taking OCs. With certain exceptions, the clinical course is benign, and there have been no reported fatalities in uncomplicated cases. The jaundice usually subsides when the drug is discontinued. A history of other liver disease, including cholestatic jaundice of pregnancy,[28,29] primary biliary cirrhosis, recurrent pruritus of pregnancy, and porphyria[30] is thought to confer added risks.

The liver is the site of biotransformation and inactivation of steroids. Constituents of oral contraceptive tablets are steroidal agents that affect the production of plasma proteins, the degree of effect depending upon the type of OC and its dosage. In large doses, estrogens have a catabolic effect; in low doses they are anabolic. Progestogens are not themselves anabolic but may potentiate the anabolic effect of estrogens. Some oral contraceptive tablets increase blood levels of thyroxine, corticosteroids and lipids by increasing carrier proteins without an elevation of the free, active form of the substances carried.[31]

(a) Biochemical and Obstructive Abnormalities in the Liver.

The significance of the changes in BSP in women using OCs is uncertain. In normal women, there is a cyclical variation of bromsulphalein retention; higher levels are noted during the luteal phase.[32] Also, healthy premenopausal women over the age of 40 may show increased BSP retention.[33]

The exact mechanism that causes a change in hepatic function in women using OCs is not known, but appears to be related partly to an impairment in the excretion of conjugated bilirubin into the canaliculi and also to reversible parenchymal hepatocellular changes. Animal experiments suggest that those steroids bearing a C-17 alpha-alkyl grouping do impair the excretion of conjugated bilirubin into the canaliculi. The degree of impairment is at least partly dose-related.[34] Progestogens alone, in the dosages normally used in oral contraception, are less likely to produce this effect. However, it is seen when progestogens are used in combination with estrogens.

Elevations of serum transaminase and alkaline phosphatase also have been reported from the use of OCs[35] and are generally considered to be due to intracanalicular obstruction.

In most instances, these abnormalities have reverted to normal when oral contraception was stopped.[36] Sometimes, persistence of treatment has been followed by a gradual return of the levels to a normal range.[30]

(b) Parenchymal Abnormalities

In women treated with OCs, changes in the endoplasmic reticulum and the mitochondria have been seen in liver biopsies examined by electron microscopy.[37] These changes were less marked in patients using combination as opposed to sequential OCs, and they were minimal and far less frequent when the subjects were given low dosage progestogens alone.[38]

In animals, progesterone causes increases in liver weight, hepatic demethylation, hepatic microsomal protein content and urinary excretion of ascorbic acid.[39] Estrogen and diethylstil bestrol significantly reduce hepatic demethylation.[40]

The jaundice reported to occur in women using OCs resembles cholestatic jaundice of pregnancy; being relatively benign, transient, and showing similar biochemical changes. There is general agreement that the clinical and biochemical changes described are rapidly reversible in most cases, probably due to the generous reserve capacity of the liver.

Alterations in Common Clinical Laboratory Tests

The oral contraceptive pill causes alterations in some of the common clinical laboratory tests. Allowance for these effects must be made when interpreting these results.

(a) **Liver Function Tests**

Bromsulphalein Retention Test	Moderate increase
SGOT and GGT	Minor increase
Alkaline Phosphatase	Variable increase
Serum Bilirubin	Increased, particularly in conditions predisposing or associated with hyperbilirubinemia.

(b) **Thyroid Function Tests**

Protein-bound Iodine (PBI) Conc.	Increased
Total Serum Thyroxine (T_4) Conc.	Increased
Triiodothyronine (T_3) Resin Uptake Test	Decreased

(c) **Adrenocortical Function Tests**

Plasma Cortisol	Increased

(d) **Coagulation Tests**

Factors II, VII, IX and X	Increased
Factor VIII	Mild increase
Platelet Aggregations	Mild increase in response to common aggregating agents.
Plasminogen	Mild increase
Antithrombin III	Mild decrease

(e) **Miscellaneous**

Serum Folate	Occasionally decreased
Glucose Tolerance Test	Abnormal

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APPENDIX I

METHODS OF ASSESSING THE EFFICACY AND UNDESIRABLE EFFECTS OF ORAL CONTRACEPTIVES

Contraceptive methods can be assessed and compared in 3 ways:

1. Analysis of fertility, morbidity and mortality rates in different populations in relation to the use of various contraceptives.

These methods are often inconclusive because of the many confounding variables and the absence of accurate estimates of contraceptive usage.

2. Cohort studies in which the fertility, morbidity and mortality of large groups are studied.

This approach has been used in the assessment of the efficacy of contraceptive techniques for several decades. The traditional method of estimating failure rates has been to use Pearl's formula:

Pregnancy rate per 100 women-years & P x 1200/M
where P = number of pregnancies
M = aggregate of all months of exposure by couples included in the investigation.

One of the flaws in this formula is that it takes no account of the change in risk with duration of use of the contraceptive.[1] It tacitly assumes that the experience of 100 women observed for 1 year can be compared with that of 50 women for 2 years or 200 women for 6 months. This is unlikely to be true. The type of woman who abandons a particular contraceptive method after a few months is likely to experience a higher failure rate than one who adheres to the technique for several years.

Alternative, more valid methods of analysis of cohort data are based upon life-table techniques.[2] These methods can be applied in various ways to assess the risks of failure for different reasons, either as single risks (gross) or competing risks (net).[3] Clinical trials of contraceptives have shown a close agreement between the Pearl Index and a cumulative 12-month life-table pregnancy rate. In the early stages of these clinical trials, the Pearl Index appeared to be superior to the short-term life-table.[4]

The chief disadvantage of the cohort approach is the large number of women required in the study to obtain precise estimates. For the assessment of efficacy, this is not an overriding disadvantage; but for the estimation of risk of rare life-threatening side effects, the numbers required are impracticable.

3. Case-control studies.

These are often used as a substitute for the more precise cohort studies when the latter are not feasible.[5] In the context of contraception, the method involves recording the number of patients with the side effect in question and comparing with matched controls. The proportions of each group, cases and controls who have used a particular contraceptive are ascertained.

The risk of the side effect among users relative to that among non-users is estimated by

$$R = \frac{\text{(cases: users) x (controls: non-users)}}{\text{(cases: non-users) x (controls: users)}}$$

Assume, for example, that 200 affected patients had used the contraceptive method believed to be a causative factor, and 150 had not done so; while 35 controls had used the method, and 315 had not. The relative risk is then

$$R = \frac{200 \times 315}{150 \times 35} = 12$$

The major advantage of this method is that relatively small numbers of patients and controls can provide significant results. The chief difficulty with the case-control method is the choice of controls. It is almost impossible to be sure that confounding variables are accounted for unless inquiry has been made for such variables, in which case compensation can be made for their presence.[6,7]

The majority of studies of the comparative efficacy and side effects of contraceptives are necessarily of the observational type where the choice of contraceptive technique for a particular woman has involved conscious selection by the physician and/or the woman herself. It is seldom feasible to mount an experiment in which women are assigned at random to 1 of 2 or more contraceptive methods. In the absence of such random allocations, the interpretation of observed differences must always be cautious, and the effect of known selective factors allowed for in the analysis wherever possible.

Since it is very difficult to distinguish between so-called "method failure" and "patient failure", the assessment of efficacy should be based upon the total pregnancy rate. In designing comparative studies, the numbers of patients included should be sufficient to detect clinically important differences in efficacy or the incidence of side effects at conventional levels of statistical significance. The required sample size must be calculated in advance for any given study.

Summary

The most efficient method of assessing the efficacy and side effects of a contraceptive is a cohort study analysed by life-table techniques. For rare side effects, where cohort studies are impracticable, a case-control comparison

provides a feasible alternative. Whatever method is used, the numbers studied should be sufficiently large to detect important differences with reasonable confidence. Particularly in the absence of random allocation of treatment, considerations must be given, in both design and analysis, to variables other than treatment that may confound the result.

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APPENDIX II

The following interim report was prepared by the Special Advisory Committee on Reproductive Physiology in March 1984, in response to reports in the medical literature which implicated the use of OCs with the development of cancer of the breast and of the cervix.

STATEMENT ON CANCER OF THE BREAST AND CERVIX IN RELATION TO THE USE OF ORAL CONTRACEPTIVES

Breast Cancer

Recently, two reports have appeared in the medical literature which suggest that there is an increased risk of breast cancer in young women under the age of 45 years who have taken OCs for several years prior to their first full-term pregnancy[1] or prior to their achieving the age of 25 years.[2]

The Special Advisory Committee on Reproductive Physiology views these papers with concern. We have studied the papers in depth, have reviewed the current literature, and have received expert advice from consultants in the field. Nearly all previously published studies have shown no overall increase in the risk of breast or other cancers in association with the use of OCs. Our committee will continue to monitor ongoing studies. On the basis of our current evaluation, however, the committee recommends the following:

1. There is no need to change current prescribing practices for OCs.
2. The lowest hormonal content consistent with effectiveness and good cycle control should be prescribed. This has been the policy of the committee since 1970.[3]
3. All women who have had prolonged usage (particularly for 4 years or more) of OCs should be encouraged to practice regular self-examination of the breasts and to have annual breast examinations by their physicians beginning at the age of 35 years.

In one of the aforementioned publications[2] an increased incidence of breast cancer and other side effects has been related to a purported high progestogenic potency of certain OCs. At the present time, however, there is no widely accepted method for determining the relative progestogenic potencies of OCs, nor is there any statistically sound evidence that contraceptive pills of different progestogenic type and dosage are deleterious or advantageous when side effects among the various brands are compared. Current suggestions supporting the use of one or other combination of an estrogen and progestogen in an OC, based upon such "potency" studies, are not accepted as scientifically valid by this committee.

Cervical Neoplasia

A recent publication[4] has raised the possibility of an increased risk of cervical neoplasia associated with the use and total duration of use of OCs. Our committee has reviewed the literature and has sought expert opinion concerning this issue. Canadian data that will be published shortly[5] do not support this concept but will confirm that the risk of cervical neoplasia is related to the number of sexual partners a woman has had and to an early age at first intercourse rather than to the use of OCs.

All women who are sexually active should have Papanicolaou smears annually to the age of 35 years. Women who are at high risk for the development of cervical neoplasia[6] should have Papanicolaou smears according to their physicians' advice.

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GUIDELINES FOR THE DIRECTIONS FOR USE OF ESTROGEN-PROGESTOGEN COMBINATION ORAL CONTRACEPTIVES

(The basis of all advertising of OCs to the medical profession from the pharmaceutical industry).

Prepared by the Special Advisory Committee on Reproductive Physiology in cooperation with the Health Protection Branch

GUIDELINES FOR THE DIRECTIONS FOR USE OF ESTROGEN-PROGESTOGEN COMBINATION ORAL CONTRACEPTIVES

INDICATION

"Prevention of Pregnancy" or "Conception Control." (For products containing less than 50 mcg of estrogen.)

For products containing 50 mcg of estrogen, the indication should be limited to the statement: "For conception control in circumstances where lower dosage estrogen formulations prove to be unacceptable."

For products containing more than 50 mcg of estrogen, the indications should be limited to therapeutic use.

CONTRA-INDICATIONS

1. Thrombophlebitis, thromboembolic disorders or a history of these conditions.
2. Cerebrovascular disorders.
3. Myocardial infarction.
4. Active liver disease.
5. History of cholestatic jaundice.
6. Known or suspected carcinoma of the breast.
7. Known or suspected estrogen-dependent neoplasia.
8. Undiagnosed abnormal vaginal bleeding.
9. Any ocular lesion arising from ophthalmic vascular disease, such as partial or complete loss of vision or defect in visual fields.
10. When pregnancy is suspected or diagnosed.

WARNINGS

1. **Predisposing Factors for Coronary Artery Diseases**

In women with predisposing factors for coronary artery disease (such as cigarette smoking, hypertension, hypercholesterolèmia, obesity, diabetes and increasing age) oral contraceptives have been reported as an additional risk factor.

After the age of 35 years, for purposes of fertility control, oral contraceptives should be considered only in exceptional circumstances and when the risk/benefit ratio has been carefully weighed by both the patient and the physician.

> Cigarette smoking increases the risk of serious adverse effects on the heart and blood vessels from oral contraceptive use. This risk increases with age and heavy smoking (15 or more cigarettes per day) and is more marked in women over 35 years of age. Women who use oral contraceptives should not smoke.

Estrogen-progestogen combinations may cause an increase in plasma lipoproteins and should be administered with caution to women known to have pre-existent hyperlipoproteinemia. Lipid profiles should be determined regularly in these patients.

The combination of obesity, hypertension and diabetes is particularly hazardous to women who are taking oral contraceptives. Should this triad of conditions develop, the patient should be placed on an alternate method of contraception.

2. Discontinue medication at the earliest manifestation of:

   A. **Thromboembolic and Cardiovascular Disorders** such as: Thrombophlebitis, pulmonary embolism, cerebrovascular disorders, myocardial ischemia, mesenteric thrombosis and retinal thrombosis.

   The use of estrogen-progestogen combination oral contraceptives should be avoided in conditions which predispose to venous stasis and to vascular thrombosis, e.g. immobilization after accidents or confinement to bed during long-term illness. Under such conditions, other non-hormonal methods of contraception should be considered. For use of oral contraceptives when surgery is contemplated, see PRECAUTIONS.

   B. **Visual Defects, Partial or Complete.**

   C. **Papilledema, or Ophthalmic Vascular Lesions.**

   D. **Severe Headache of Unknown Etiology.**

3. Fetal abnormalities have been reported to occur in the offspring of women who have taken estrogen-progestogen combinations in early pregnancy. Rule out pregnancy as soon as it is suspected.
4. The use of oral contraceptives during the period a mother is breastfeeding her infant may not be advisable. The hormonal components are excreted in breast milk and may reduce its quantity and quality. The long-term effects on the developing child are not known.
5. This drug may cause fluid retention. Conditions such as epilepsy, asthma, and cardiac or renal dysfunction require careful observation.

PRECAUTIONS

1. **Physical Examination and Follow-up**

Before oral contraceptives are used, a thorough history and physical examination should be made,

including a blood pressure determination. Breasts, liver, extremities and pelvic organs should be examined. A Papanicolaou smear should be taken if the patient has been sexually active and a urinalysis should be done.

The first follow-up examination should be done 3 months after oral contraceptives are prescribed. Thereafter, examinations should be made at least once a year, more frequently for those patients at greater risk for adverse effects. At each annual visit, examination should include those procedures outlined above that were done at the initial visit.

2. **Hepatic Function**

Patients who have had jaundice should be given oral contraceptives with great care and under close observation.

If there is a clear-cut history of cholestatic jaundice, especially if it occurred during pregnancy, other methods of contraception should be prescribed. The development of severe generalized pruritus or icterus requires that the medication be withdrawn until the problem is resolved.

If the jaundice should prove to be cholestatic in type, the use of oral contraceptives should not be resumed. In patients taking oral contraceptives, changes in the composition of the bile may occur and an increased incidence of gallstones has been reported. Hepatic nodules (adenoma and focal nodular hyperplasia) have been reported, particularly in long-term users of oral contraceptives. Although these lesions are uncommon, they have caused fatal intra-abdominal hemorrhage and should be considered in women presenting with an abdominal mass, acute abdominal pain, or evidence of intra-abdominal bleeding.

3. **Hypertension**

Patients with essential hypertension whose blood pressure is well-controlled may be given the drug but only under close supervision. If a significant elevation of blood pressure in previously normotensive or hypertensive subjects occurs at any time during the administration of the drug, cessation of medication is necessary.

4 **Migraine and Headache**

The onset or exacerbation of migraine or the development of headache of a new pattern which is recurrent, persistent or severe, requires discontinuation of oral contraceptives and evaluation of the cause.

5. **Diabetes**

Diabetic patients, or those with a family history of diabetes, should be observed closely to detect any alterations in carbohydrate metabolism. Patients predisposed to diabetes who can be kept under close supervision may be given oral contraceptives. Young diabetic patients whose disease is of recent origin, well-controlled, and not associated with hypertension or other signs of vascular disease such as ocular fundal changes, should be closely observed.

6. **Metabolic and Endocrine Diseases**

In metabolic or endocrine diseases and when metabolism of calcium and phosphorus is abnormal, careful clinical evaluation should precede medication and a regular follow-up is recommended.

7. **Ocular Disease**

Progressive astigmatic error, possibly leading to keratoconus, has been noted in some myopic women receiving oral contraceptives. In women who developed myopia at or near puberty, and in whom myopia stabilized in adult life, oral contraceptives after some 6 months of use have increased the refractive error 2 to 3-fold. Women with a family history of myopic astigmatism or keratoconus who are using oral contraceptives may experience rapid advancement of the ocular disorder.

Contact lens wearers who develop visual changes or changes in lens tolerance should be assessed by an ophthalmologist and temporary or permanent cessation of wear considered.

8. **Connective Tissue Disease**

The use of oral contraceptives in some women has been associated with positive lupus erythematous cell tests and with clinical lupus erythematosus. In some instances exacerbation of rheumatoid arthritis and synovitis have been observed.

9. **Breasts**

Although oral contraceptive use has not been shown to increase the risk of developing breast cancer, particular attention should be paid to women who have an immediate family history of this disease and are therefore more prone to its development. Careful monitoring is mandatory because, if a breast cancer should develop, estrogen-containing drugs may cause a rapid progression if the malignancy is hormone-dependent.

Special judgement should be used in prescribing oral contraceptives for women with fibrocystic disease of the breast.

Women receiving oral contraceptives should be instructed in self-examination of their breasts. Their physicians should be notified whenever any masses are detected.

10. **Vaginal Bleeding**

Persistent irregular vaginal bleeding requires special diagnostic judgement to exclude the possibility of pregnancy or neoplasm. If these can be excluded, prescribing a product containing a higher dosage of estrogen may correct the problem.

11. **Fibroids**

Patients with fibroids (leiomyomata) should be carefully observed. Sudden enlargement, pain, or tenderness require discontinuance of medication.

12. **Age**

In general, women in the later reproductive years gradually assume an increasing risk of circulatory and metabolic complications which becomes more prominent at 35 years of age. In view of this, closer observation, shorter duration of oral contraceptive use and avoidance of cigarette smoking is advisable. Alternatively, adoption of other means of birth control should be considered for this age group.

Oral contraceptives may mask the onset of the climacteric.

13. **Emotional Disorders**

Patients with a history of emotional disturbances, especially the depressive type, are more prone to have a recurrence of depression while taking oral contraceptives. In cases of a serious recurrence, a trial of an alternate method of contraception should be made which may help to clarify the possible relationship.

14. **Laboratory Tests**

Laboratory test-results should not be considered reliable unless oral contraceptive therapy has been discontinued for 2 to 4 months because therapy may alter the following determinations and possibly mask underlying disease;

A. **Liver function tests**

Bromsulphalein retention — increased. SGOT — variously reported elevations. Alkaline phosphatase and gamma GT — slightly elevated.

B. **Coagulation tests**

Elevation of test values reported for such parameters as prothrombin and Factors VII, VIII, IX and X. Increased platelet aggregation. Decreased antithrombin III.

C. **Thyroid function tests**

Protein binding of thyroxine is increased as indicated by increased PBI and total serum thyroxine concentrations and decreased T_3 resin uptake.

D. **Adrenocortical function tests**

Plasma cortisol is increased. Reported impaired adrenocortical response is now attributed to accelerated metapyrone conjugation by estrogen.

E. **Reproductive endocrine profile changes**

Luteinizing hormone — the mid-cycle surge is suppressed.
Pregnanediol — suppressed.
Serum prolactin — may be elevated.

F. **Other tests**

Increase in:

Phospholipids and triglycerides
Cryofibrinogen
Ceruloplasmin
Cholinesterase
Haptoglobulins
Transferrin
Plasminogen
alpha-2-macroglobulin
Testosterone binding globulin
Estrogen binding globulin
Angiotensinogen
Aldosterone secretion rate
Serum magnesium, copper, or zinc
Iron binding capacity

Decrease in:

Orosomucoid
Serum folate
Serum cyanocobolamin
Serum pyridoxine (disturbed tryptophan metabolism)
Glucose tolerance (temporary)

Variable changes:

Lipoprotein cholesterol fractions! The clinical relevance of those alterations that have been reported to be statistically significant has yet to be demonstrated.

15. **Tissue Specimens**

Pathologists should be advised of oral contraceptive therapy when specimens obtained from surgical procedures are submitted for examination.

16. **Return to Fertility**

After discontinuing oral contraceptive therapy, the patient should delay pregnancy until at least one normal spontaneous cycle has occurred. An alternate contraceptive method should be used during this time.

17. **Amenorrhea**

Women having a history of oligomenorrhea, secondary amenorrhea, or irregular cycles may remain anovulatory or become amenorrheic following estrogen-progestogen combination therapy.

Amenorrhea, especially if associated with breast secretion, that continues for 6 months or more after withdrawal, warrants a careful assessment of hypothalamic-pituitary function.

18. **Thromboembolic Complications — Post-surgery**

Retrospective studies have reported an increased risk of post-surgery thromboembolic complications in oral contraceptive users. If feasible, oral contraceptives should be discontinued and a non-hormonal method substituted at least one month prior to elective major surgery. Oral contraceptives should not be resumed until at least two weeks after hospital discharge following surgery.

19. **Drug Interactions**

A. Concurrent use of the following drugs may result in reduced contraceptive reliability and increased incidence of breakthrough bleeding:

Ampicillin
Analgesics
Antimigraine preparations
Chloramphenicol
Isoniazid
Neomycin
Nitrofurantoin
Penicillin V
Phenylbutazone
Sulfonamides
Tetracycline

B. Concurrent use of anticoagulants with oral contraceptives may reduce the anticoagulant effect.

C. Effectiveness of the following drugs may be altered when used concurrently with oral contraceptives:

Antihypertensives
Hypoglycemics
Tricyclic antidepressants
Vitamins

D. Concurrent use of the following drugs may reduce contraceptive reliability because of accelerated estrogen metabolism caused by the induction of hepatic enzymes:

Carbamazepine
Phenobarbital
Phenytoin
Primidone
Rifampicin

ADVERSE REACTIONS

An increased risk of the following serious adverse reactions has been associated with the use of oral contraceptives:

Thrombophlebitis
Pulmonary embolism
Mesenteric thrombosis
Neuro-ocular lesions, e.g., retinal thrombosis and optic neuritis
Myocardial infarction
Cerebral thrombosis
Cerebral hemorrhage
Hypertension
Benign hepatic tumors
Gallbladder disease
Congenital anomalies

The following adverse reactions also have been reported in patients receiving oral contraceptives:

Nausea and vomiting, usually the most common adverse reaction occurring in approximately 10% or less of patients during the first cycle. Other reactions, as a general rule, are seen less frequently or only occasionally.

Gastrointestinal symptoms (such as abdominal cramps and bloating)
Breakthrough bleeding
Spotting
Change in menstrual flow
Dysmenorrhea
Amenorrhea during and after treatment
Temporary infertility after discontinuance of treatment
Edema
Chloasma or melasma which may persist
Breast changes: tenderness, enlargement, and secretion
Change in weight (increase or decrease)
Endocervical hyperplasias
Possible diminution in lactation when given immediately post-partum
Cholestatic jaundice
Migraine
Increase in size of uterine leiomyomata
Rash (allergic)
Mental depression
Reduced tolerance to carbohydrates
Vaginal candidiasis
Premenstrual-like syndrome
Intolerance to contact lenses
Change in corneal curvature (steepening)
Cataracts
Optic neuritis
Retinal thrombosis
Changes in libido
Chorea
Changes in appetite
Cystitis-like syndrome
Rhinitis
Headache
Nervousness
Dizziness
Hirsutism
Loss of scalp hair
Erythema multiforme
Erythema nodosum
Hemorrhagic eruption
Vaginitis
Porphyria
Impaired renal function
Raynaud's phenomenon
Auditory disturbances
Hemolytic uremic syndrome
Pancreatitis

PACKAGE INSERT FOR PATIENTS USING ORAL CONTRACEPTIVES
and
SUPPLEMENTARY INFORMATION BOOKLET FOR PATIENTS CONSIDERING THE USE OF ORAL CONTRACEPTIVES

Prepared by The Special Advisory Committee on Reproductive Physiology in cooperation with the Health Protection Branch.

PACKAGE INSERT FOR PATIENTS USING ORAL CONTRACEPTIVES

You should know that a supplementary information booklet which describes the benefits and risks of taking oral contraceptives is available from your doctor or pharmacist. Be sure to obtain a copy and read it carefully before you start taking oral contraceptives.

(Product Name) is an oral contraceptive preparation which contains 2 female sex hormones (give names and dosages) in a specific ratio. It has been shown to be highly effective in preventing pregnancy when taken as prescribed by your doctor.

You should know that, as with other medications, this product should not be used by certain women. In a small number of others, potentially serious adverse effects may occur. Your doctor is in the best position to decide whether or not any conditions are present that pose a risk to you.

Who Should Not Take Oral Contraceptives ("The Pill")

There are several groups of women who should not use birth control pills. You should not use the pill if you have or have had any of the following conditions:

Unusual vaginal bleeding that has not yet been diagnosed.
Blood clots in the legs, lungs, eyes or elsewhere.
A stroke, heart attack or chest pain (angina pectoris).
Known or suspected cancer of the breast or sex organs.
Liver tumor associated with the use of the pill or other estrogen-containing products.
Jaundice or liver disease if still present.

The pill should not be taken if you are pregnant or if pregnancy is suspected.

You should know that cigarette smoking increases the risk of serious adverse effects on the heart and blood vessels from oral contraceptive use. This risk increases with age and heavy smoking (15 or more cigarettes a day) and is more marked in women over 35 years of age. Women who use oral contraceptives should not smoke.

When You Are Taking Oral Contraceptives

If you and your doctor have elected for you to use (Product Name) for the prevention of pregnancy, you should be aware that periodic medical supervision is necessary.

1. Take the tablets only on the advice of your doctor and carefully follow all directions given to you. It is important to take the tablets exactly as prescribed, otherwise you may become pregnant.
2. After the age of 35 years, it is generally inadvisable to use oral contraceptives. Your doctor should be consulted in this regard.
3. Contact your doctor at least once a year after the initial visits.
4. **You should be alert for signs of serious adverse effects and call your doctor immediately if they occur:**

   Sharp pain in the chest, coughing blood or sudden shortness of breath (indicating a possible blood clot in the lung).
   Pain in the calf (indicating a possible blood clot in the leg).
   Crushing chest pain or heaviness (indicating a possible heart attack).
   Sudden severe headache or vomiting, dizziness or fainting, disturbance of vision or speech, or weakness or numbness in an arm or leg (indicating a possible stroke).
   Sudden partial or complete loss of vision (indicating a possible blood clot in the eye).
   Severe pain or lump in the abdomen (indicating a possible tumor of the liver).
   Severe depression.
   Yellowing of the skin (jaundice).
   Unusual swelling of the extremities.
   Breast lumps (you should ask your doctor for advice and instructions on how to examine your own breasts regularly).
5. Oral contraceptives should never be taken if you think you are pregnant. They will not prevent the pregnancy from continuing and may interfere with the normal development of the baby.
6. If you wish to become pregnant, your doctor may recommend that you discontinue the use of the pill and delay pregnancy until at least one spontaneous menstrual cycle has occurred. Contact your doctor for advice on this and for recommendations on alternate methods of contraception that may be used during this time.
7. Consult your doctor before resuming the use of oral contraceptives after childbirth, miscarriage or therapeutic abortion. Hormones in oral contraceptives are known to appear in the milk and may decrease its flow.
8. If for any reason you should require elective surgery, the surgeon should be informed that you are using oral contraceptives so that you can be correctly advised about discontinuing their use one month before surgery and substituting another contraceptive method.

9. If you have occasion to see a different physician, be sure to inform him or her that you are taking contraceptive pills.

10. It is important to inform your doctor if you are taking, or if you start to take, any other medication (prescription or non-prescription drugs) because this may alter the effectiveness and/or cycle-control of oral contraceptives.

SUPPLEMENTARY INFORMATION BOOKLET FOR PATIENTS CONSIDERING THE USE OF ORAL CONTRACEPTIVES

INTRODUCTION

The purpose of this booklet is to provide information to help you make an informed decision on whether or not to choose oral contraceptives as your method of birth control (contraception).

Whether you are in the process of making a decision on which method of birth control you wish to use or have already decided that you want to use oral contraceptives (birth control pills or "the pill") **be sure that you read this booklet carefully.**

Oral contraceptives are the most effective way (except for sterilization) to prevent pregnancy. They also may be used for therapeutic purposes. They are convenient and, for most women, free of serious or unpleasant side effects. **Oral contraceptives, like other potent medication, always must be taken under the continuous supervision of a physician.**

There is some risk associated with the use of any medication and oral contraceptives are no exception. If you are thinking about using an oral contraceptive, it is important that you understand the risks involved. You should discuss these risks with your physician before taking the pill. Although oral contraceptives have important advantages over other methods of contraception, they have certain risks that no other method has, and some of these risks may continue after you have stopped using the pill. Only you can decide whether the advantages are worth the risks.

Your physician is the best person to explain to you the consequences of these risks. However, this leaflet will help you to understand the most important risks. **It will explain how you can help your doctor prescribe the pill as safely as possible by telling him or her about yourself and being alert for the earliest signs of possible trouble.**

If you do not understand any part of this booklet, if you want further information on other birth control methods, or if you are concerned that you should not use the birth control pill, please contact your physician to discuss your questions and concerns.

WHAT ORAL CONTRACEPTIVES ARE AND HOW THEY WORK

There are two types of birth control pills which may be dispensed on a doctor's prescription.

1. The most common type is the "combination pill" which contains synthetic forms of two female sex hormones, an estrogen and a progestogen. The amounts and types of estrogen and progestogen vary from one preparation to another, but the amount of estrogen is most important because both the effectiveness and some of the dangers of oral contraceptives are mainly related to the amount of estrogen.
2. The second type, often called the "mini-pill," contains a synthetic form of only one female sex hormone, a progestogen.

The birth control pill works by doing the following things in the woman:

(a) It inhibits the monthly release of an egg by the ovaries.

(b) It changes the mucus produced by the cervix so that the movement of sperm through the mucus (and hence into the uterus or womb) is slowed down.

(c) Should an egg be released by the ovary, the birth control pill acts both to slow down the movement of the egg in the Fallopian tubes and to decrease the ability of the sperm to penetrate into (and thus fertilize) the egg.

EFFECTIVENESS OF ORAL CONTRACEPTIVES

When the amount of estrogen is 30 to 35 micrograms or more, and the pill is taken as directed, combination oral contraceptives are 98% to more than 99% effective (i.e. there would be approximately one pregnancy if 100 women used the pill for one year).

The mini-pill (progestogen only) is slightly less effective (96% to 97%) than the combination oral contraceptives.

OTHER WAYS TO PREVENT PREGNANCY

As this booklet will explain, oral contraceptives have several serious risks. Some other methods of contraception have lesser risks. They are usually less effective than oral contraceptives, but, used properly, may be effective enough for many women. The following table gives reported pregnancy rates (the number of women out of 100 who would become pregnant in one year) for these methods:

PREGNANCIES PER 100 WOMEN PER YEAR

Intrauterine device (IUD), 1-6;
Diaphragm with spermicidal products (creams or jellies), 2-20;
Condom (rubber), 3-36;
Aerosol foams, 2-29;
Jellies and creams, 4-36;
Periodic abstinence (rhythm) all types, 1-47;
—Calendar method, 14-47;
—Temperature method, 1-20;
—Temperature method — intercourse only in post-ovulatory phase, 1-7;
—Mucus method, 1-25;
No contraception, 60-80.

The figures (except for the IUD) vary widely because people differ in how well they use each method. Very faithful users of the various methods may achieve pregnancy rates in the lower ranges of those given above, which are the average results for large groups of women. Other women may expect pregnancy rates more in the middle of these ranges. Except for the IUD, effective use of these methods requires somewhat more effort than simply taking a single pill every evening, but it is an effort that many couples undertake successfully.

WHO SHOULD NOT USE ORAL CONTRACEPTIVES

There are several groups of women who should not use birth control pills. You should not use the pill if you have or have had any of the following conditions:

- Unusual vaginal bleeding that has not yet been diagnosed.
- Blood clots in the legs, lungs, eyes or elsewhere.
- A stroke, heart attack or chest pain (angina pectoris).
- Known or suspected cancer of the breast or sex organs.
- Liver tumor associated with the use of the pill or other estrogen-containing products.
- Jaundice or liver disease if still present.

The pill should not be taken if you are pregnant or if pregnancy is suspected.

CONDITIONS THAT YOUR DOCTOR WILL WANT TO WATCH CLOSELY OR THAT MIGHT CAUSE YOUR DOCTOR TO RECOMMEND A METHOD OF CONTRACEPTION OTHER THAN ORAL CONTRACEPTIVES.

- Irregular or scanty menstrual periods before starting to take the pill. If you have these or you are a young woman without a regular menstrual cycle, an alternate method of contraception may be advisable because if you use the pill, you may have difficulty resuming normal menstrual cycles or becoming pregnant after discontinuing the use of the pill.
- Breast Conditions:
  - Breastfeeding
  - A family history of breast cancer
  - Breast disorders including pain, discharge from the nipples, thickenings, or lumps. In some circumstances, benefit may be derived from taking the pill, while in others, adverse effects may follow.
- Diabetes
- High blood pressure
- Abnormal levels of fats in the bloodstream (high cholesterol or triglycerides)
- Cigarette smoking
- Migraine headaches
- Heart or kidney disease
- Epilepsy
- Mental depression
- Fibroid tumors of the uterus
- Gallbladder or pancreatic disease
- Asthma
- Problems during a prior pregnancy
- Plans for forthcoming surgery
- History of jaundice or other liver disease

THE RISKS OF ORAL CONTRACEPTIVES

1. **Circulatory disorders (including blood clots in the legs, lungs, heart, eyes or brain)**

   Blood clots are the most common of the serious side effects of oral contraceptives. A clot can result in a stroke (if the clot is in the brain), a heart attack (if the clot is in a blood vessel of the heart), a pulmonary embolus (a clot which forms in the legs or pelvis, then breaks off and travels to the lungs), or damage to or loss of a limb (a clot in a blood vessel in or leading to an arm or leg). Any of these can cause death or disability. Clots also occur rarely in the blood vessels of the eye, resulting in blindness or impairment of vision in that eye.

There is evidence that the risk of clotting increases with higher estrogen doses. **It is therefore important to keep the dosage of estrogen as low as possible, so long as the oral contraceptive used has an acceptable pregnancy rate and doesn't cause unacceptable changes in the menstrual pattern.**

While the risk of blood clots increases with age in both pill-users and non-users, the increased risk from the pill appears to be constant at all ages.

Cigarette smoking by pill-users increases the possibility of serious circulatory disorders. This risk increases with age and heavy smoking (15 or more cigarettes per day) and becomes quite marked in women over 35 years of age. For this reason, women who use the pill, particularly those over 30 years of age, should not smoke.

The chances of a woman developing serious circulatory problems while taking the pill are shown in the following table.

Circulatory Problem	Incidence in pill-users
*Thrombophlebitis (blood clot(s) and inflammation of leg veins(s))	1 in 10 000 (3 times higher than for non-users)
*Thromboembolism (blood clot(s) in the lung(s))	1 in 30 000 (4 times higher than for non-users)
*Stroke	1 in 30 000 (3 times higher-than for non-users)
*Heart attack (women over 35 who smoke)	1 in 5000 (3 times higher-than for non-users)

*In some cases these may be fatal.

Heart attacks in women who do not use oral contraceptives are more common in the presence of such risk factors as age, high blood pressure, high cholesterol, obesity, diabetes or cigarette smoking. In the absence of any of these factors, the use of the pill may double the risk of heart attack. However, the combination of cigarette smoking (especially heavy smoking) and the pill greatly increases the possibility of heart attack. Pill-users who smoke are about 10 times more likely to have a heart attack than non-users who do not smoke. If they have additional risk factors, the chance of having a heart attack may be considerably greater.

In addition to blood clots, studies have shown that women taking oral contraceptives are twice as likely as non-users to have a rupture of a blood vessel in the brain.

There is evidence that some of the effects on the circulatory system may persist for a time after the use of the pill is discontinued.

2. **Formation of tumors**

When certain animals are given the female sex hormone, estrogen (an ingredient of the pill), continuously for long periods, cancers may develop in the breast, cervix, vagina and liver. This suggests that oral contraceptives may cause cancer in humans. However, studies to date in women taking currently marketed oral contraceptives have not confirmed that oral contraceptives cause cancer in humans.

Women who have a strong family history of breast cancer or who have breast nodules or thickenings, or discharge from the nipple, must be examined frequently by their doctors if they choose to use oral contraceptives instead of other methods of contraception. This also applies to those who were exposed to DES (diethylstilbestrol), an estrogen, while their mothers were pregnant with them. Many studies have shown that pill-users have a lesser risk of benign breast disease than non-users. There remains no evidence, however, that the oral contraceptives currently available (containing estrogen and progestogen in combination, or progestogen alone) increase the risk of breast cancer.

There is evidence that women who use or have used the pill have less chance of developing cancer of the endometrium (lining of the womb) or ovary.

One study reported malignant melanoma (a type of skin cancer), urinary tract cancer and thyroid cancer more frequently in pill-users than in non-users.

Benign (non-malignant) or malignant liver tumors, which may occur rarely, have been associated with short-term as well as long-term use of oral contraceptives. The former do not spread, but they may rupture and produce internal bleeding, which may cause death.

3. **Dangers to a developing child if oral contraceptives are used during or immediately preceding pregnancy**

Oral contraceptives should not be taken by pregnant women because they may damage the developing child. An increased risk of heart and limb defects has been associated with the use of sex hormones, including oral contraceptives, during pregnancy. In addition, the developing female child whose mother has received DES (diethylstilbestrol), an estrogen, during pregnancy, has a risk of developing cancer of the vagina or cervix in her teens or young adulthood. abnormalities of the urinary tract and sex organs have been reported in male offspring so exposed. It is possible, although this has not been demonstrated, that other estrogens such as those in oral contraceptives could have the same effect in the child if the mother takes them during pregnancy.

There is no evidence to suggest that taking oral contraceptives immediately preceding pregnancy will adversely affect the development of a baby. However, when a woman stops taking oral contraceptives to become pregnant, her doctor may recommend an alternate method of contraception for a short while.

4. **Gallbladder disease**

Women who use oral contraceptives have a greater risk than non-users of having gallbladder disease requiring surgery. The increased risk may first appear within one year of use and may double after 4 or 5 years of use.

5. **Other side effects of oral contraceptives**

Some pill-users experience unpleasant side effects that may be temporary and not hazardous to health. There may be tenderness of the breasts, nausea and vomiting, weight gain or loss, and swelling of the ankles. A spotty darkening of the skin, particularly of the face, is possible and may persist. Many of these effects are seen more frequently with combination oral contraceptives containing 50 micrograms or more of estrogen. Unexpected vaginal bleeding or spotting, or changes in the usual menstrual period, may occur. Irregular bleeding is frequently seen when using the mini-pill (progestogen only). This also occurs with combination oral contraceptives containing less than 50 micrograms of estrogen but it usually disappears after the first few cycles. It is not an indication to stop taking the pill prior to consulting a doctor.

More serious side effects include worsening of migraine, asthma, epilepsy, and kidney or heart disease caused by the tendency for water to be retained in the body when oral contraceptives are used. Other side effects are growth of pre-existing fibroid tumors of the

uterus, mental depression and liver problems with jaundice (yellowing of the skin). The amounts of sugar and fatty substances in the blood may be elevated; the long-term effects of these changes are not known. Some pill-users develop high blood pressure which may persist after stopping the pill. High blood pressure may lead to serious disease of the kidney and circulatory system. Frequent measurement of blood pressure is needed if there is a history of toxemia of pregnancy, kidney disease or increased blood pressure.

Other reactions have been reported occasionally. These include more frequent urination and some discomfort when urinating, kidney disease, including kidney failure with blood cell breakdown, nervousness, dizziness, an increase in or loss of hair, an increase or decrease in sex drive, appetite changes, cataracts, and a need for a change in contact lens prescription or inability to use contact lenses.

After stopping oral contraceptives, the ability to menstruate or become pregnant may be delayed. This is especially true for women who have had irregular menstrual cycles prior to the use of oral contraceptives. As discussed previously, it is wise to delay attempting pregnancy for a short time.

THE RISKS OF ORAL CONTRACEPTIVES COMPARED TO THE RISKS OF OTHER BIRTH CONTROL METHODS

The many studies on the risks of oral contraceptives and other methods of contraception have been analyzed to estimate the risk of death associated with each. **This risk has two parts**: (a) **the risk of the method itself** (e.g. the risk that oral contraceptives will cause death due to abnormal clotting), and (b) **the risk of death due to pregnancy in the event the method fails.**

The risk of death per 100 000 women each year for various contraceptive methods is shown in the following table. The figures are based upon present knowledge, and new information could alter these. It should be remembered that these risks are composed of two parts, as just described.

Risk of Death per 100 000 Women per Year Due to Method and Pregnancy

Method of Contraception	Age Group (years) 15-24	25-34	35-44
No method	7.2	12.0	27.0
Pill - non-smoker	0.6	1.6	23.0
Pill - smoker	3.0	10.2	84.5
IUD	1.2	1.3	2.0
Condom	1.4	0.4	0.4
Diaphragm, spermicide	1.6	1.2	2.5
Rhythm	2.0	1.6	3.2

This table shows that the risk of death from the various methods of contraception is low and below that associated with using no method of contraception, except for pill-users over 35 who smoke. For example, the risk of death from unintended pregnancy in women who use no method of contraception is about 8 times that in non-smokers up to the age of 35 years who are using oral contraceptives. Also, at any age the risk of death, due to unexpected pregnancy resulting from the use of other methods of contraception, is generally similar or less than that from the use of oral contraceptives.

The number of deaths attributed to pill use each year could be reduced to about one-seventh if no pill-users smoked and none took the pill after her 35th birthday.

For comparison, the risks of death per 100 000 women each year is about 5 for tubal ligation (sterilization) and about 1 to 4 per 100 000 for therapeutic abortion in early pregnancy.

NON-CONTRACEPTIVE BENEFITS OF ORAL CONTRACEPTIVES

Although there are risks associated with the use of the birth control pill, there are also certain health advantages (other than contraception) that have been reported.

1. The combination birth control pill may reduce the incidence of cancer of the endometrium (lining of the womb) and ovaries. Although estrogen **alone** may increase the likelihood of developing cancer of the endometrium, the combination of an estrogen and a progestogen appears to be protective for both the uterus and ovaries. For example, the birth control pill is estimated to cause (in the U.S.A.) about 500 deaths each year (in women of any age and including smokers) but 850 deaths from ovarian cancer each year may be prevented by its use.
2. The pill may reduce the likelihood of developing benign breast disease.
3. The pill may reduce the likelihood of development of cysts of the ovaries.
4. The pill seems to have a protective effect against infections of the Fallopian tubes and pelvic inflammatory disease. These are serious infections that can cause infertility or ectopic (tubal) pregnancy.
5. Pill-users have less blood loss during menstrual periods and have more regular cycles. This reduces the chance of developing iron-deficiency anemia.
6. The use of birth control pills may decrease the severity of menstrual cramps or pain (dysmenorrhea) and premenstrual syndrome (PMS).

PERIODIC EXAMINATION

A complete medical and family history is necessary before oral contraceptives are prescribed. At that time, after about three months, and then annually, an examina-

tion particularly of blood pressure, breasts, abdomen, pelvic organs and limbs is generally conducted. It is usual to have a Pap smear and a urinalysis initially and at the yearly examination.

IF YOU DECIDE TO TAKE ORAL CONTRACEPTIVES

Should you and your doctor decide that, for you, the benefits of the birth control pill outweigh its risks, you should be aware that periodic medical supervision is necessary.

> You should know that cigarette smoking increases the risk of serious adverse effects on the heart and blood vessels from oral contraceptive use. This risk increases with age and heavy smoking (15 or more cigarettes a day) and is more marked in women over 35 years of age. Women who use oral contraceptives should not smoke.

1. Take the tablets only on the advice of your doctor and carefully follow all directions given to you. It is important to take the tablets exactly as prescribed, otherwise you may become pregnant.
2. After the age of 35 years, it is generally inadvisable to use oral contraceptives. Your doctor should be consulted in this regard.
3. Contact your doctor at least once a year after the initial visits.
4. **You should be alert for signs of serious adverse effects and call your doctor immediately if they occur:**

   Sharp pain in the chest, coughing blood, or sudden shortness of breath (indicating a possible blood clot in the lung).

   Pain in the calf (indicating a possible blood clot in the leg).

   Crushing chest pain or heaviness (indicating a possible heart attack).

   Sudden severe headache or vomiting, dizziness or fainting, disturbance of vision or speech, or weakness or numbness in an arm or leg (indicating a possible stroke).

   Sudden partial or complete loss of vision (indicating a possible blood clot in the eye).

   Severe pain or lump in the abdomen (indicating a possible tumor of the liver).

   Severe depression.

   Yellowing of the skin (jaundice).

   Unusual swelling of the extremities.

   Breast lumps (you should ask your doctor for advice and instructions on how to examine your own breasts regularly).
5. Oral contraceptives should never be taken if you think you are pregnant. They will not prevent the pregnancy from continuing and may interfere with the normal development of the baby.
6. If you wish to become pregnant, your doctor may recommend that you discontinue the use of the pill and delay pregnancy until at least one spontaneous menstrual cycle has occurred. Contact your doctor for advice on this and for recommendations on alternate methods of contraception that may be used during this time.
7. Consult your doctor before resuming the use of oral contraceptives after childbirth, miscarriage, or therapeutic abortion. Hormones in oral contraceptives are known to appear in the milk and may decrease its flow.
8. If for any reason you should require elective surgery, the surgeon should be informed that you are using oral contraceptives so that you can be correctly advised about discontinuing their use one month before surgery and substituting another contraception method.
9. If you have occasion to see a different physician, be sure to inform him or her that you are taking contraceptive pills.
10. It is important to inform your doctor if you are taking, or if you start to take, any other medication (prescription or non-prescription drugs) because this may alter the effectiveness and/or cycle control of oral contraceptives.